الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guideline on Good Pharmacovigilance Practices (GVP)

Version 4.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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What is New in version no. 4.0?

The following table shows the update to the previous version:

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MODULE II – PHARMACOVIGILANCE SYSTEM MASTER FILE	63	**Add:** II.C.3.2.4. National PSSF section on "computerized systems and databases"
MODULE V – RISK MANAGEMENT SYSTEMS	135	**Update:** V.B.10.9. RMP annex 9: Saudi-Specific Annex (SSA)
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MODULE VI – COLLECTION, MANAGEMENT AND SUBMISSION OF REPORTS OF SUSPECTED ADVERSE REACTIONS TO MEDICINAL PRODUCTS	173	**Add:** VI.C.2.1.1. Spontaneous reports
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MODULE VII – PERIODIC BENEFIT RISK EVALAUTION REPORT/ PERIODICSAFETY UPDATE REPORT (PBRER/PSUR) VII.B.5.3. PSUR/PBRER section "Actions taken in the reporting interval for safety reasons"	205	**Delete** Submission of comprehensive signal evaluation report of potential signal based on SFDA request.

MODULE VII – PERIODIC BENEFIT RISK EVALAUTION REPORT/ PERIODICSAFETY UPDATE REPORT (PBRER/PSUR)	235	**Add:** VII.C.1. Standard submission schedule of PSUR/PBRERs
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MODULE I- PHARMACOVIGILANCE SYSTEMS AND THEIR QUALITY SYSTEM

1.A. INTRODUCTION

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

The definition of a pharmacovigilance system is a system used by the MAH and by The Saudi Food and Drug Authority (SFDA) to fulfil the tasks and responsibilities listed in this guideline and designed to monitor the safety of authorized medicinal products and detect any change to their benefit-risk balance. The SFDA likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.

For performing their pharmacovigilance activities, MAHs, and the SFDA shall establish and use quality systems that are adequate and effective for this performance.

By following the overall quality objectives in I.B.4 and the guiding principle in I.B.5 to meet the needs of patients, healthcare professionals and the public in relation to the safety of medicines, the application of the quality system should be adapted to how crucial each pharmacovigilance task is for fulfilling the quality objectives for each medicinal product covered by a quality system.

In this Module, 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”.

I.B. STRUCTURES AND PROCESSES

I.B.1. Pharmacovigilance system

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

A pharmacovigilance system, like any system, is characterized by its structures, processes and

outcomes. For each specific pharmacovigilance process, including its necessary structures, a dedicated Module is included in GVP.

I.B.2. Quality, quality objectives, quality requirements and quality system

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

In general terms, quality is a matter of degree and can be measured. Measuring if the required degree of quality has been achieved necessitates pre-defined quality requirements. Quality requirements are those characteristics of a system that are likely to produce the desired outcome, or quality objectives. The overall quality objectives for pharmacovigilance systems are provided under I.B.4.

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

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

I.B.3. Quality cycle

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

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

I.B.4. Overall quality objectives for pharmacovigilance

The overall quality objectives of a pharmacovigilance system are:

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

I.B.5. Principles for good pharmacovigilance practices

With the aim of fulfilling the overall quality objectives in I.B.4, the following principles should guide the design of all structures and processes as well as the conduct of all tasks and responsibilities:

- The needs of patients, healthcare professionals and the public in relation to the safety of medicines should be met;
- Upper management should provide leadership in the implementation of the quality system and motivation for all staff members in relation to the quality objectives;
- All persons within the organization should be involved in and support the pharmacovigilance system based on task ownership and responsibility in a degree according to their tasks and assigned responsibilities;
- All persons involved with the entire organization should engage in continuous quality improvement following the quality cycle in I.B.3;
- Resources and tasks should be organized as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance;
- All available evidence on the benefit-risk balance of medicinal products should be sought and all relevant aspects, which could impact on the benefit-risk balance and the use of a product, should be considered for decision-making;

- Good cooperation should be fostered between MAHs, the SFDA, public health organizations, patients, healthcare professionals, learned societies and other relevant bodies in accordance with the applicable legal provisions;

I.B.6. Responsibilities for the quality system within an organization

A sufficient number of competent and appropriately qualified and trained personnel shall be available for the performance of pharmacovigilance activities. Their responsibility should include adherence to the principles defined in I.B.5.

For the purpose of a systematic approach towards quality in accordance with the quality cycle (see I.B.3.), managerial staff (i.e. staff with management responsibilities) in any organization should be responsible for:

- Ensuring that the organization documents the quality system as described in I.B.11;
- Ensuring that the documents describing the quality system are subject to document control in relation to their creation, revision, approval and implementation;
- Ensuring that adequate resources are available, and that training is provided (see I.B.7);
- Ensuring that suitable and sufficient premises, facilities and equipment are available (see I.B.8);
- Ensuring adequate compliance management (see I.B.9);
- Ensuring adequate record management (see I.B.10.);
- Reviewing the pharmacovigilance system including its quality system at regular intervals in risk-based manner to verify its effectiveness (see I.B.12.) and introducing corrective and preventive measures where necessary;
- Ensuring that mechanisms exist for timely and effective communication, including escalation processes of safety concerns relating to medicinal products within an organization;
- Identifying and investigating concerns arising within an organization regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- Ensuring that audits are performed (see I.B.12).

In relation to the management responsibilities described above, upper management within an

organization should provide leadership through:

- Motivating all staff members, based on shared values, trust and freedom to speak and act with responsibility and through recognition of staff members' contributions within the organization; and
- Assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organization.

I.B.7. Training of personnel for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organization is intrinsically linked with the availability of a sufficient number of competent and appropriately qualified and trained personnel (see I.B.6.).

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

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

The training should support continuous improvement of relevant skills, the application of scientific progress and professional development and ensure that staff members have the appropriate qualifications, understanding of relevant pharmacovigilance requirements as well as experience for the assigned tasks and responsibilities. All staff members of the organization should receive and be able to seek information about what to do if they become aware of a safety concern.

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

Adequate training should also be considered by the organization for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of

pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, terminologies, sales and marketing, regulatory affairs, legal affairs and audits.

Appropriate instructions on the processes to be used in case of urgency, including business continuity (see I.B.11.3.), shall be provided by the organization to their personnel.

I.B.8. Facilities and equipment for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes is also intrinsically linked with appropriate facilities and equipment used to support the processes. Facilities and equipment should include office space, information technology (IT) systems and (electronic) storage space. They should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance (see I.B.4.) also be available for business continuity (see I.B.11.3.). Facilities and equipment which are critical for the conduct of pharmacovigilance (see I.B.11.3.) should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. There should be processes in place to keep awareness of the valid terminologies (see Module VI) in their valid versions and to keep the IT systems up-to-date accordingly.

I.B.9. Specific quality system procedures and processes

I.B.9.1. Compliance management by the MAHs

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

- The continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and that appropriate measures are taken by the MAH (see Modules IX and XII);
- The scientific evaluation of all information on the risks of medicinal products as regards patients' or public health, in particular as regards adverse reactions in human beings arising from use of the product within or outside the terms of its marketing authorization or associated with occupational exposure (see Modules VI, VII, VIII, IX);

- The submission of accurate and verifiable data on serious and non-serious adverse reactions to the SFDA within the legally required time-limits (see Modules VI and IX);
- The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions and to validate signals (see Modules V, VI, VII, VIII and IX);
- Effective communication by the MAH with the SFDA, including communication on new or changed risks (see Module XV), the pharmacovigilance system master file (PSMF) (see Module II), risk management systems (see Module V), risk minimizations measures (see Modules V and XVI), periodic safety update reports/periodic benefit risk evaluation report (PSUR/PBRERs) (see Module VII), corrective and preventive actions (see Modules II, III and IV) and post-authorization safety studies (see Module VIII);
- The update of product information by the MAH in the light of scientific knowledge;
- Appropriate communication of relevant safety information to healthcare professionals and patients (see Module XV)

I.B.9.2. Compliance management by the SFDA

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

- Ensuring the evaluation of the quality, including completeness, of pharmacovigilance data submitted;
- Ensuring the assessment of pharmacovigilance data and its processing in accordance with the legal timelines;
- Ensuring independence in the performance of pharmacovigilance activities;
- ensuring effective communication with patients, healthcare professionals, MAHs and the general public;
- Conducting inspections, including pre-authorization inspections.

Independence in the performance of pharmacovigilance activities is interpreted in the sense that all regulatory decisions on medicinal products should be taken in the sole interest of patients' and public health.

I.B.10. Record management

The organization shall record all pharmacovigilance information and ensure that it is handled and stored so as to allow accurate reporting, interpretation and verification of that information.

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

The record management system should support:

- The management of the quality of pharmacovigilance data, including their completeness, accuracy and integrity;
- Timely access to all records;
- Effective internal and external communication; and
- The retention of documents relating to the pharmacovigilance systems and the conduct of pharmacovigilance for individual medicinal products, in accordance with the applicable retention periods.

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

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

There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period. The record management system should be described in a record management policy.

I.B.11. Documentation of the quality system

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

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

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

- Quality objectives specific to their organizations in accordance with the overall quality objectives provided under I.B.4. and the structure- and process-specific quality objectives in accordance with each Module of GVP; and
- Methods for monitoring the effectiveness of the pharmacovigilance system (see I.B.12.).

The quality system shall be documented by:

- Documents on organizational structures and assignments of tasks to personnel (see I.B.11.1.);
- Training plans and records (see I.B.7.);
- Instructions for the compliance management processes (see I.B.9.);
- Appropriate instructions on the processes to be used in case of urgency, including business continuity (see I.B.11.2.);
- Performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities;
- Reports of quality audits and follow-up audits, including their dates and results.

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

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

- The methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;

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

I.B.11.1. Additional quality system documentation by MAHs

In addition to the quality system documentation in accordance with I.B.11., MAHs shall document:

- Their human resource management in the PSMF (see Module II);
- Job descriptions defining the duties of the managerial and supervisory staff;
- An organizational chart defining the hierarchical relationships of managerial and supervisory staff ;
- Instructions on critical processes (see I.B.11.2.) in the PSMF (see Module II); and
- Their record management system in the PSMF (see Module II).

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

For the requirements of documenting the quality system in the PSMF or its annexes, see Module II.

I.B.11.2. Critical pharmacovigilance processes and business continuity

The following pharmacovigilance processes should be considered as critical include:

- Continuous safety profile monitoring and benefit-risk evaluation of authorized medicinal products;
- Establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimization;

- Collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- Signal management;
- Scheduling, preparation (including data evaluation and quality control), submission and assessment of PSUR/PBRERs;
- Meeting commitments and responding to requests from the SFDA, including provision of correct and complete information;
- Interaction between the pharmacovigilance and product quality defect systems;
- Communication about safety concerns between MAHs and the SFDA, in particular notifying changes to the benefit-risk balance of medicinal products;
- Communicating information to patients and healthcare professionals about changes to the benefit-risk balance of products for the aim of safe and effective use of medicinal products;
- Keeping product information up-to-date with the current scientific knowledge, including the conclusions of the assessment and recommendations from the SFDA;
- Implementation of variations to marketing authorizations for safety reasons according to the urgency required.

Business continuity plans should be established in a risk-based manner and should include:

- Provisions for events that could severely impact on the organization's staff and infrastructure in general or on the structures and processes for pharmacovigilance in particular; and
- Back-up systems for urgent exchange of information within an organization, amongst organizations sharing pharmacovigilance tasks as well as between MAHs and the SFDA.

I.B.12. Monitoring of the performance and effectiveness of the pharmacovigilance system and its quality system

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

- Reviews of the systems by those responsible for management;

- audits;
- Compliance monitoring;
- Inspections;
- Evaluating the effectiveness of actions taken with medicinal products for the purpose of minimizing risks and supporting their safe and effective use in patients.

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

The requirements for the quality system itself are laid out in this Module and its effectiveness should be monitored by managerial staff, who should review the documentation of the quality system (see I.B.11.) at regular intervals, with the frequency and the extent of the reviews to be determined in a risk-based manner. Pre-defined programs for the review of the system should therefore be in place. Reviews of the quality system should include the review of standard operating procedures and work instructions, deviations from the established quality system, audit and inspections reports as well as the use of the indicators referred to above.

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

As a consequence of the monitoring of the performance and effectiveness of a pharmacovigilance system and its quality system (including the use of audits), corrective and preventive measures should be implemented when deemed necessary. In particular, as a consequence of audits, corrective action(s), including a follow-up audit of deficiencies, shall

be taken where necessary. Guidance on compliance monitoring for each pharmacovigilance process is provided in each Module of GVP as appropriate.

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

I.B.13. Preparedness planning for pharmacovigilance in public health emergencies

Any pharmacovigilance system should be adaptable to public health emergencies and preparedness plans should be developed as appropriate.

For preparedness planning in the KSA, see I.C.3.

I.C. OPERATION OF PHARMACOVIGILANCE IN KSA

I.C.1. Overall pharmacovigilance responsibilities of the applicant and MAH in KSA

The MAH in KSA is 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 MAH 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 MAH 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 PSMF and be maintained by the MAH for all authorized medicinal products (see Module II). The applicant or the MAH is also responsible for developing and maintaining product-specific risk management systems (see Module V).

Guidance on the structures and processes on how the MAH should conduct the pharmacovigilance tasks and responsibilities is provided in the respective GVP Modules.

I.C.1.1. Responsibilities of the MAH in relation to the qualified person responsible for pharmacovigilance in KSA

Each Pharmacovigilance system can have only one local QPPV. The local QPPV must be a full-time qualified person responsible for pharmacovigilance (QPPV) who resides in KSA. A local QPPV must be employed one marketing authorization holder for their Pharmacovigilance system. In case the local QPPV is responsible for multiple marketing authorization holder Pharmacovigilance system, it requires a specific pre-authorized by the SFDA for shared or separate pharmacovigilance systems or may fulfill the role of QPPV for more than one pharmacovigilance system of the same marketing authorization holder provided that the QPPV can fulfill all obligations. Moreover, any Marketing Authorization Holder (MAH) must register their full-time QPPV and Deputy through the Saudi Vigilance System platform. This registration must include an official MAH memo to the local QPPV, official contact details having names of the QPPV and Deputy and pharmacovigilance training certificates and their qualifications.

Moreover, upon the resignation of the qualified person responsible for pharmacovigilance (QPPV) from any pharmaceutical companies in Saudi Arabia, the MAH must notify SFDA-NPC when the QPPV sign the resignation letter. In addition, the MAH needs to notify the SFDA-NPC with all the contact and official information of the newly qualified person responsible for pharmacovigilance (QPPV) within **90 days** after the notification. During the notification period, the deputy in the MAH shall take all the responsibilities in following up the pharmacovigilance activities until the new official qualified person responsible for pharmacovigilance (QPPV) is appointed to handle the pharmacovigilance activities in Saudi Arabia.

Information relating to the QPPV shall be included in the PSMF (see Module II).

As part of the pharmacovigilance system, the marketing authorization holder may have permanently and continuously at its disposal a backup for the qualified person responsible for pharmacovigilance (Deputy QPPV) who resides in KSA and preferably a Saudi citizen. The marketing authorization holder shall submit the name and contact details of the deputy to the SFDA, in any changes relayed to the information should submitted in accordance with the regulation on the SFDA variations guidelines,

The duties of the local QPPV and the Deputy QPPV shall be defined in a job description. In

addition, the hierarchical relationship of the Deputy QPPV ought to be defined in an organizational chart together with those of other managerial and supervisory staff. Information relating to the Saudi Deputy QPPV shall be included in the pharmacovigilance systems master file (PSMF). Overall, the marketing authorization holder should ensure that structures and processes are in place so that the Saudi Deputy QPPV can fulfill the responsibilities listed in I.C.1.3.

In order to do this, the MAH should ensure that mechanisms are in place so that the local QPPV receives all relevant information and that the local QPPV can access all information the QPPV considers relevant, in particular on:

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

The outcome of the regular reviews of the quality system referred to in I.B.6. and I.B.12. and the measures introduced should be communicated by the managerial staff to the QPPV.

Compliance information should be provided to the QPPV on a periodic basis. Further, such information may used to provide assurance to the local QPPV that commitments in the framework of RMPs and post-authorization safety systems are being adhered to.

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

In particular with regard to its adverse reaction database (or other systems to collate adverse reaction reports), the MAH should implement a procedure to ensure that the local QPPV can have access and can obtain information from the MAH database. For instance, for responding

to urgent requests from the SFDA, at any time. If this procedure requires the involvement of other personnel, such as, database specialists that have to considered in the arrangements made by the MAH for supporting the local QPPV outside of normal working hours.

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

When a MAH intends to establish a partnership with another MAH, organization or person that has a direct or indirect impact on the pharmacovigilance system, the local QPPV should be informed early enough and be involved in the preparation of the corresponding contractual arrangements (see I.C.1.5.). Therefore, all necessary provisions relevant to the pharmacovigilance system are included.

I.C.1.2. Qualifications of the qualified person responsible for pharmacovigilance in KSA

The MAH shall ensure that the local Saudi QPPV has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. The QPPVs should have a minimum of a bachelor's degree in pharmacy or medicine. Moreover, the QPPVs should have training every **two** years in Pharmacovigilance, epidemiology, and have to be licensed by Saudi Commission for Health Specialties. The training must cover at least pharmacovigilance competencies as following:

Topic
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
Introduction to pharmaco-epidemiology
Biostatistics
Basics of signal detection
Medical Aspects of Adverse Drug Reactions
Risk benefit assessment in Pharmacovigilance
National pharmacovigilance regulations
PSUR/PBRER overview
RMP overview
PSMF overview
Risk communication, DHPC

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

The expectation is that the applicant or MAH will assess the qualification of the QPPV prior to appointment by, for example, reviewing university qualifications, knowledge of KSA Pharmacovigilance requirements, experience in pharmacovigilance and local contact details for the local QPPV.

The applicant or MAH should provide the local QPPV with training in relation to its pharmacovigilance system, which is appropriate for the role prior to the QPPV taking up the position, which is appropriately documented. Consideration should be given to additional training, as needed, of the QPPV in the medicinal products covered by the pharmacovigilance system.

In case for any MAHs would like to designate a deputy for the QPPV, it’s recommended for the MAHs to assign an employee with adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. In addition, any Deputy QPPV should have a minimum of bachelor's degree in pharmacy or medicine, basic training in pharmacovigilance science, and should be licensed by Saudi Commission for Health Specialties. The applicant or marketing authorization holder should provide the Deputy QPPV with training about its pharmacovigilance system, which is appropriate for the role before the Deputy QPPV taking

up the position and which is appropriately documented.

I.C.1.3. Role of the qualified person responsible for pharmacovigilance in KSA

The QPPV appointed by the MAH shall be appropriately qualified (see I.C.1.2.) and shall be at the MAH's disposal permanently and continuously (see I.C.1.1.). Backup policy and procedure in the case of absence of the QPPV have to be in place and should be accessible through the QPPV's contact details. The QPPV should ensure that the backup person has all necessary information, training, and credential to fulfill the role.

The local QPPV shall be responsible for the establishment and maintenance of the MAH's pharmacovigilance system and therefore should have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements. Hence, the QPPV must have immediate access to the PSMF (see Module II) and be in a position of authority to ensure and to verify that the information contained in the PSMF is an accurate and up-to-date reflection of the pharmacovigilance system under the QPPV's responsibility.

In relation to the medicinal products covered by the pharmacovigilance system, specific additional responsibilities of the QPPV should include:

- Creation of the local standard operating procedures (SOPs) to handling all the pharmacovigilance activities (e.g. back-up and delegation, Training, handling of local ICSRs, causality assessment, seriousness, PSMF/PSSF preparation and updating files, literature review for the local journals, risk minimization measures handling, Signal management per KSA specifications, and PSUR/PBRER preparation and submission per KSA specifications) to be compatible accordance with the regulation on the SFDA variations guidelines and the MAH must be involved of the local QPPV in all the Pharmacovigilance activities .
- Involved of the local QPPV in the causality assessment, seriousness, submission and follow-up of the local ICSRs.
- Having an overview of medicinal product safety profiles and any emerging safety concerns;
- Having awareness of any conditions or obligations adopted as part of the marketing authorizations and other commitments relating to safety or the safe use of the products;

- Having awareness of risk minimization measures;
- Being aware of and having sufficient authority over the content of RMPs;
- Being involved in the review and sign-off of protocols of post-authorization safety studies conducted in KSA or pursuant to an RMP agreed in KSA;
- Having awareness of post-authorization safety studies requested by the SFDA including the results of such studies;
- Ensuring conduct of pharmacovigilance and submission of all pharmacovigilance-related documents in accordance with the legal requirements and GVP;
- Ensuring the necessary quality, including the correctness and completeness, of pharmacovigilance data submitted to the SFDA;
- Ensuring a full and prompt response to any request from the SFDA for the provision of additional information necessary for the benefit-risk evaluation of a medicinal product;
- Providing any other information relevant to the benefit-risk evaluation to the SFDA;
- Providing input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and communication to patients and healthcare professionals);
- Acting as a single pharmacovigilance contact point for the SFDA on a 24-hour basis and as a contact point for pharmacovigilance inspections.

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

The QPPV may delegate specific tasks, under supervision to appropriately qualified and trained individuals within the same organization For instance, acting as safety experts'

products, if the QPPV maintains system oversight and overview of the safety profiles of all products. Such delegation should be documented.

I.C.1.4. Specific quality system processes of the MAH in KSA

In applying, the requirements set out in I.B.9.1. in KSA, the MAH shall put in place the following additional specific quality system processes for ensuring:

- The submission of adverse reaction data to National Pharmacovigilance Centre (NPC) within the legal timelines;
- The monitoring of the use of terminology in either systematically or by regular random evaluation;
- The retention of minimum elements of the PSMF (see Module II) as long as the system described in the PSMF exists and for at least further 5 years after it has been formally terminated by the MAH;
- The retention of pharmacovigilance data and documents relating to individual authorized medicinal products as long as the marketing authorization exists and for at least further 10 years after the marketing authorization has ceased to exist;
- That the product information is kept up-to-date by the MAH in the light of scientific knowledge.

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

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

Documents transferred in situations where the business of the MAH is taken over by another organization should be complete.

I.C.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the MAH

The marketing authorization holder may subcontract the pharmacovigilance system to third parties. The Third Parties must be authorized from SFDA to provide the Pharmacovigilance services. The Third Parties must get the pre-authorized approval before sign any contract with any MAHs to provide the Pharmacovigilance services.

This subcontract cannot be official until taking the final approval from SFDA after reviewing the contract and the pharmacovigilance documents. The marketing authorization holder shall nevertheless retain full responsibility for the completeness and accuracy of the pharmacovigilance system master file (PSMF) (see Module II). The ultimate responsibility for the fulfilment of all pharmacovigilance tasks and responsibilities and the quality and integrity of the pharmacovigilance system always remains with the marketing authorization holder.

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

When subcontracting tasks to another organization, the marketing authorization holder shall draw up subcontracts and these should be detailed, up-to-date, and clearly document the contractual arrangements between the marketing authorization holder and the other organization, describing arrangements for delegation and the responsibilities of each party. A description of the subcontracted activities (Specific Pharmacovigilance activities) and/or services shall be included in the pharmacovigilance system master file (PSMF) and a list of the subcontracts shall be included in an annex to the PSMF, specifying the product(s) concerned (see Module II).

An organization, which will be subcontracted for specific pharmacovigilance activities, will be subject to pre-authorization pharmacovigilance inspections by the SFDA. Contractual arrangements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. When preparing contractual arrangements, the marketing authorization holder should include sufficiently detailed descriptions of the delegated tasks, the related interactions, and data exchange, together with, for example, agreed

definitions, tools, assignments, and timelines. The contractual arrangements should also contain clear information on the practical management of pharmacovigilance as well as related processes, including those for the maintenance of pharmacovigilance databases. Further, they should indicate which processes are in place for checking whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, regular risk-based audits of the other organization by the marketing authorization holder or introduction of other methods of control and assessment are recommended. For responsibilities of the marketing authorization holder towards the QPPV in this context, see I.C.1.1.

I.C.2. Role of the SFDA

I.C.2.1. General Role of the SFDA and the role of the SFDA's secretariat

The role of the SFDA is to coordinate the monitoring of medicinal products for human use authorized in KSA and to provide advice on the measures necessary to ensure their safe and effective use, in particular, by coordinating the evaluation and implementation of legal pharmacovigilance requirements and the monitoring of such implementation. The tools established and maintained by the SFDA for the coordination are presented in the GVP Modules for each process.

I.C.2.2. Role of the Pharmacovigilance Advisory Committee

The role of the Pharmacovigilance advisory committee is to provide advice on the safety of medicinal products 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 SFDA for products available in KSA. 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 by SFDA, and all other sources
2. Investigation of adverse reactions
3. Regularly review and monitoring of safety concerns
4. Discussion of emerging safety concerns at the request of the SFDA
5. Discussion of PSUR/PBRER reports at the request of the SFDA

6. Recommendations to the SFDA on benefit-risk evaluations and actions necessary to minimize risk and maximize benefit
7. Providing advice to the SFDA on safety, enabling effective risk identification, assessment and management in the pre- and post-authorization phase.

I.C.2.3. Specific quality system processes of the quality systems of the SFDA

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

- Monitoring and validating the use of terminology either systematically or by regular random evaluation
- Assessing and processing pharmacovigilance data in accordance with the timelines provided by legislation;
- Ensuring effective communication within the SFDA in accordance with the provisions on safety announcements (see Module XV);
- Arranging for the essential documents describing their pharmacovigilance systems to be kept as long as the system exists and for at least further 5 years after they have been formally terminated;
- Ensuring that pharmacovigilance data and documents relating to individual authorized medicinal products are retained as long as the marketing authorization exists or for at least further 10 years after the marketing authorization has expired.

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

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

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

Documents can be retained in electronic format, provided that the electronic system has been appropriately validated and appropriate arrangements exist for system security, access and back-up of data. If pharmacovigilance documents in paper format are transferred into an electronic format, the transfer process should ensure that all of the information present in the original format is retained in a legible manner and that the media used for storage will remain readable over time. The legal requirements for record management (see I.B.10.)

In addition to the above, the SFDA shall establish procedures for collecting and recording all

suspected adverse reactions that occur in their territory (see Module VI).

In addition to the above, the SFDA shall establish procedures for literature monitoring

In addition to the quality system documentation in accordance with I.B.11. and I.B.11.2., the SFDA shall clearly determine, and to the extent necessary, keep accessible the organizational structures and the distribution of tasks and responsibilities as well as establish contact points, in particular to facilitate interaction between the SFDA, MAHs and persons reporting information on the risks of medicinal products as regards patients' or public health.

Quality audits of the SFDA's pharmacovigilance systems shall be performed according to a common methodology. The results of audits shall be reported by the SFDA (see Module IV).

I.C.3. Preparedness planning in KSA for pharmacovigilance in public health emergencies

The pharmacovigilance systems of MAHs and the SFDA should be adaptable to public health emergencies. Preparedness plans should be developed as appropriate (see I.B.13.).

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

Pharmacovigilance requirements for public health emergencies should be considered by the SFDA on a case-by-case basis and appropriately notified to MAHs and the public. The SFDA publishes its notifications on the SFDA website.

MODULE II – PHARMACOVIGILANCE SYSTEM MASTER FILE

II.A. INTRODUCTION

The PSMF defined as a detailed description of the pharmacovigilance system used by the MAH with respect to one or more authorized medicinal products, and the minimum requirements for its content and maintenance are set out in the annex 1. The detailed requirements provided by the Commission Implementing Regulation are further supported by the guidance in this Module of the Good Vigilance Practice(s).

The PSMF shall be located either at the site in the KSA where the main pharmacovigilance activities of the MAH are performed or at the site in the KSA where the QPPV operates.

It is a requirement of the marketing authorization application that summary information about the pharmacovigilance system is submitted to the SFDA. This summary includes information on the location of the PSMF (see II.B.2.1). There is no requirement for variations for changes in the content of the PSMF, refer to the variation guideline.

This Module provides detailed guidance regarding the requirements for the PSMF, including its maintenance, content and associated submissions to SFDA.

II.B. STRUCTURES AND PROCESSES

The PSMF is a legal requirement in the KSA. This guidance concerns the requirements for the PSMF and is applicable for any medicinal product authorized in the KSA, irrespective of the marketing authorization procedure. The required content and management of the PSMF applies irrespective of the organizational structure of a MAH, including any subcontracting or delegation of activities, or their location. Irrespective of the location of other activities, the QPPV's residence, the location at which he/she performs his/her tasks and the PSMF location must be within the KSA.

The content of the PSMF should reflect global availability of safety information for medicinal products authorized in the KSA, presenting information on the pharmacovigilance system applied at global, regional and local levels.

II.B.1. Objectives

The PSMF shall describe the pharmacovigilance system and support/document its compliance

with the requirements. PSMF shall also contribute to the appropriate planning and conduct of audits by the applicant or marketing authorizations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by SFDA. The PSMF provides an overview of the pharmacovigilance system, which may be requested and assessed by the SFDA during marketing authorization application(s) or post-authorization.

Through the production and maintenance of the PSMF, the MAH and the QPPV should be able to:

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

II.B.2. Registration and maintenance

II.B.2.1. Summary of the applicant's pharmacovigilance system

The MAH should include a summary of the pharmacovigilance system in the authorization application. The summary should include the following elements in module 1.6.1 of the dossier:

- QPPVs must be free fulltime for Pharmacovigilance activities and the local QPPV must be register at SFDA QPPV website registration form.
- Official Contact details of the qualified person such as official email having name or QPPV and Deputy
- Statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in this GVP module.
- Reference to the location where the pharmacovigilance system master file for the medicinal product is kept

Applicants for, and holders of, simplified registrations of traditional herbal or homeopathic and medicinal products are not required to submit a pharmacovigilance system summary,

however, they are required to operate a pharmacovigilance system, to prepare, maintain and make available on request a PSMF.

For other herbal medicinal products, not falling within the scope of the traditional-use registration, the requirements to operate a pharmacovigilance system, to prepare, maintain and make available on request a PSMF and to submit a summary of the pharmacovigilance system apply.

For homeopathic medicinal products registered via the simplified registration procedure the requirements to operate a pharmacovigilance system, to maintain and make available on request a PSMF and to submit a summary of the pharmacovigilance system do not apply.

For other homeopathic medicinal products, not falling within the scope of the simplified registration, the requirements to operate a pharmacovigilance system, to prepare, maintain and make available on request a PSMF and to submit a summary of the pharmacovigilance system apply.

II.B.2.2. Location

The PSMF shall be located within the KSA, either at the site where the main pharmacovigilance activities are performed or at the site where the QPPV operates, irrespective of the format (paper-based or electronic format file) and the local QPPV must have an access to the PSMF file (having a copy of it) and the local QPPV is the owner for the local PSSF. If the PSMF in electronic format, the address will mentioned clearly that it is virtual document located in such sharing point or site, can be accessed by such personnel (specify the positions that authorized to have an access).

Any change to the location shall be notified immediately to the SFDA. The required location information for the PSMF is a physical office address of the MAH or a contracted third party. Where the PSMF is held in electronic form, the location stated must be a site where the data stored can be directly accessed, and this is sufficient in terms of a practical electronic location.

II.B.2.3. Transfers of responsibilities for the PSMF

The pharmacovigilance system may change with time. Transfer or delegation of responsibilities and activities concerning the master file should be documented (see II.B.4.2. and II.B.4.8.) and managed to ensure that the MAH fulfils their responsibilities. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the PSMF

should also be notified to the QPPV in order to support their authority to make improvements to the system. The types of changes that should be routinely and promptly notified to the QPPV are:

Updates to the PSMF or its location that are notified to the SFDA;

The addition of corrective and/or preventative actions to the PSMF (e.g. following audits and inspections). The QPPV should also be able to access information about deviations from the processes defined in the quality management system for pharmacovigilance;

- Changes to content that fulfil the criteria for appropriate oversight of the pharmacovigilance system (in terms of capacity, functioning and compliance);
- Changes in arrangements for the provision of the PSMF to the SFDA;
- Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR/PBRER production);
- Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
- Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications, studies.

Any recipient QPPV should explicitly accept the following changes in writing such as transfer of responsibility for a pharmacovigilance system to a QPPV.

The QPPV should be in a position to ensure and to verify that the information contained in the PSMF is an accurate and up to date reflection of the pharmacovigilance system under his/her responsibility (see Module I).

II.B.3. The representation of pharmacovigilance systems

The PSMF, shall describe the pharmacovigilance system for one or more medicinal products of the MAH. For different categories of medicinal products, the MAH may, if appropriate, apply separate pharmacovigilance systems. Each such system shall be described in a separate PSMF. Those files shall cumulatively cover all medicinal products of the MAH for which a marketing authorization has been issued or an authorization has been granted.

It is anticipated that there will be circumstances where a single MAH may establish more than one pharmacovigilance system e.g. specific systems for particular types of products (vaccines, consumer health, etc.), or that the pharmacovigilance system may include products from more

than one MAH. In either case, a single and specific PSMF shall be in place to describe each system.

A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the PSMF.

Where a pharmacovigilance system is shared by several MAHs, each MAH is responsible ensuring that a PSMF exists to describe the pharmacovigilance system applicable for his products, and this should be approved by the SFDA. For a particular product(s) the MAH may delegate through preauthorized written agreement (e.g. to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the MAH is responsible. In this case the PSMF of the MAH may cross refer to all or part of the PSMF managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the MAH and the SFDA. The MAH should be able to assure the content of the referenced file(s) in relation to the pharmacovigilance system applicable to their product(s). Activities for maintaining the PSMF in a current and accessible state can be delegated.

Where applicable, a list of all PSMFs held by the same MAH shall be provided in the annex (see II.B.4.8.); this includes their location(s), details of the responsible QPPV(s) and the relevant product(s).

Submission of summary information to the SFDA cannot contain multiple locations for a single PSMF. The address of the location of the PSMF should be an office address which reflects the site in the KSA.

When delegating any activities concerning the pharmacovigilance system and its master file, the MAH retains ultimate responsibility for the pharmacovigilance system, submission of information about the PSMF location, maintenance of the PSMF and its provision to the SFDA upon request. Detailed written agreements describing the roles and responsibilities for PSMF content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, should be in place.

When a pharmacovigilance system is shared, it is advised that the partners agree on how to mutually maintain the relevant sections within their own PSMFs. Accessibility of the PSMF to all the applicable MAH(s), and its provision to the SFDA should be defined in written agreements. It is vital that MAH(s) can gain assurance that the pharmacovigilance system used for its products is appropriate and compliant.

II.B.4. Information to be contained in the PSMF

The PSMF shall include documents to describe the pharmacovigilance system. The content of the PSMF should reflect the global availability of safety information for medicinal products authorized in the KSA. The content shall be indexed to allow for efficient navigation around the document and follow the modular system described in the following sections and the annex headings described in II.B.6.1. The main principle for the structure of the content of the PSMF is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it should be referred to and contained in the annexes. The control associated with change of content is described in section II.B.5.

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

II.B.4.1. PSMF section on qualified person responsible for pharmacovigilance (QPPV)

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

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

- A description of the responsibilities guaranteeing that the qualified person has sufficient authority over the pharmacovigilance system in order to promote, maintain and improve compliance;
- A summary curriculum vitae with the key information on the role of the QPPV, including proof of registration with the NPC.
- Official contact details.
- Details of back-up arrangements to apply in the absence of the QPPV.
- A list of tasks that have been delegated by the QPPV shall also be included in the annexes (see II.B.4.8.). This should outline the activities that are delegated and to whom and include the access to a medically qualified person if applicable (Module I). This list may be supplied as a copy of a written procedural document provided the required content is covered.

The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance (including registration with the NPC). The contact details supplied should include name, postal address, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a MAH address.

II.B.4.2. PSMF section on the organizational structure of the MAH

A description of the organizational structure of the MAH relevant to the pharmacovigilance system must be provided. The description should provide a clear overview of the companies involved, the main pharmacovigilance departments and the relationship(s) between organizations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. Specifically, the PSMF shall describe:

- The organizational structure of the MAH(s), showing the position of the QPPV in the organization.
- The site(s) where the pharmacovigilance functions are undertaken covering ICSR collection, evaluation, safety database case entry, PSUR/PBRER production, signal detection and analysis, RMP management, pre- and post-authorization study management, and management of safety variations to product particulars.

Diagrams may be particularly useful; the name of the department or third party should be indicated.

Delegated activities

The PSMF, where applicable, shall contain a description of the delegated activities and/or services relating to the fulfilment of pharmacovigilance obligations. This includes arrangements with other parties in any country, worldwide.

Links with other organizations, such as co-marketing agreements and contracting of pharmacovigilance activities should be outlined. A description of the location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s) and territories. The list should be organized according to; service providers (e.g. medical information, auditors, patient support program providers, study data management etc.), commercial arrangements (distributors, licensing

partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.). Individual contractual agreements shall be made available at the request of the SFDA or during inspection and audit and the list provided in the Annexes (see II.B.4.8.).

II.B.4.3. PSMF section on the sources of safety data

The description of the main units for safety data collection should include all parties responsible, on a global basis, for solicited and spontaneous case collection for products authorized in the KSA. This should include medical information sites as well as affiliate offices and may take the form of a list describing the country, nature of the activity and the product(s) (if the activity is product specific) and providing a contact point (address, telephone and e-mail) for the site. The list may be located in the Annexes of the PSMF. Information about third parties (license partners or local distribution/marketing arrangements) should also be included in the section describing contracts and agreements (see II.B.4.2. and II.B.4.8.).

Flow diagrams indicating the main stages, timeframes and parties involved may be used. However, represented, the description of the process for ICSRs from collection to reporting to the SFDA should indicate the departments and/or third parties involved.

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

II.B.4.4. PSMF section on computerized systems and databases

The location, functionality and operational responsibility for computerized systems and databases used to receive, collate, record and report safety information and an assessment of

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

II.B.4.5. PSMF section on pharmacovigilance processes

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

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

- Continuous monitoring of product benefit-risk profile(s) applied and the result of evaluation and the decision-making process for taking appropriate measures; this should include signal generation, detection and evaluation. This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc.;
- Risk management system(s) and monitoring of the outcome of risk minimization measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements;
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;

- PSUR/PBRER scheduling, production and submission, if applicable (see Module VII);
- Communication of safety concerns to consumers, healthcare professionals and the national medicines authorities;
- Implementation of safety variations to the summary of product characteristics (SPC) and patient information leaflets (PIL); procedures should cover both internal and external communications.

In each area, the MAH should be able to provide evidence of a system that supports appropriate and timely decision making and action.

The description must be accompanied by the 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 MAH;
2. The scientific evaluation by the MAH 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 authorities 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 signals;
5. Effective communication by the MAH with the national medicines authorities, including communication on new risks or changed risks, the PSMF, risk management systems, risk minimization measures, PSUR/PBRERs, corrective and preventive actions, and post-authorization studies;
6. The update of product information by the MAH in the light of scientific knowledge, and on the basis of a continuous monitoring by the MAH of information released by the national medicines authorities;
7. Appropriate communication by the MAH of relevant safety information to healthcare professionals and patients.

These interfaces with other functions include, but are not limited to, the roles and

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

II.B.4.6. PSMF section on pharmacovigilance system performance

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

- An explanation of how the correct reporting of ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting over the past year;
- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by the SFDA regarding the quality of ICSR reporting, PSUR/PBRERs or other submissions;
- An overview of the timeliness of PSUR/PBRER reporting to the SFDA (the annex should reflect the latest figures used by the MAH to assess compliance);
- An overview of the methods used to ensure timeliness of safety variation submissions compared the SFDA deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance system shall be described and

explained. A list of performance indicators must be provided in the Annex to the PSMF, alongside the results of (actual) performance measurements.

II.B.4.7. PSMF section on quality system

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

Document and Record Control

A description of the archiving arrangements for electronic and/or hardcopy versions of the PSMF should be provided, as well as an overview of the procedures applied to other quality system and pharmacovigilance records and documents (see also Module I).

Procedural documents

- A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc.), and the controls that are applied to their accessibility, implementation and maintenance.
- Information about the documentation systems applied to relevant procedural documents under the control of third parties.

A list of specific procedures and processes related to the pharmacovigilance activities and interfaces with other functions, with details of how the procedures can be accessed must be provided, and the detailed guidance for the inclusion of these is in section II.B.4.5.

Training

- A description of the resource management for the performance of pharmacovigilance activities. The organizational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organizational structure (see II.B.4.3)
- Information about sites where the personnel are located (this is described under sections II.B.4.2 and II.B.4.3) whereby the sites are provided in the PSMF in relation to the organization of specific pharmacovigilance activities and in the Annexes, which provide the list of site contacts for sources of safety data. However, a description should be provided in order to explain the training organization in relation to the personnel and site information;

- A summary description of the training concept, including a reference to the location training files.

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

Auditing

Information about quality assurance auditing of the pharmacovigilance system should be included in the PSMF. A description of the approach used to plan audits of the pharmacovigilance system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the pharmacovigilance system maintained in the annex referred to II.B.4.8. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the obligations and cover a rolling 5-year period.

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

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the PSMF should also describe the process for recording, managing and resolving deviations from the quality system. The master file shall also document deviations from pharmacovigilance procedures, their impact and management until resolved. This may be

documented in the form of a list referencing a deviation report, and its date and procedure concerned.

II.B.4.8. Annex to the PSMF

An annex to the PSMF shall contain the following documents:

- A list of medicinal products covered by the PSMF including the name of the medicinal product, the international non-proprietary name of the active substance(s). The list should be organized per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimization measures contained in the RMP or laid down as conditions of the marketing authorization, non-standard PSUR/PBRER periodicity). The monitoring information may be provided as a secondary list.

For marketing authorizations that are included in a different pharmacovigilance system, for example, because the MAH has more than one pharmacovigilance system or third party agreements exist to delegate the system, reference to the additional PSMF(s) should also be provided as a separate list in the Annexes, such that, for a MAH, the entire product portfolio can be related to the set of PSMFs.

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

- A list of contractual agreements covering delegated activities including the medicinal products.
- A list of tasks that have been delegated by the qualified person for pharmacovigilance.
- A list of all completed audits, for a period of five years, and a list of audit schedules.
- Where applicable, a list of performance indicators.
- Where applicable, a list of other PSMFs held by the same MAH. This list should include the PSMF number(s), and the name of MAH of the QPPV responsible for the pharmacovigilance system used. If the pharmacovigilance system is managed by another party that is not an MAH, the name of the service provider should also be included.

The MAH shall record in the logbook any alteration of the content of the PSMF made within the last five years. Also, the MAH shall indicate in the logbook the date, the person responsible for the alteration and, where appropriate, the reason for the alteration, and other change control documentation as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change.

II.B.5 Change control, logbook, versions and archiving

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

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

In addition to these changes being documented in the PSMF for the purpose of change control (in the logbook), the QPPV should always been kept informed of these changes.

Changes to the PSMF should be recorded, such that a history of changes is available (specifying the date and the nature of the change), changes to the PSMF must be recorded in the logbook. Descriptive changes to the content of the master file must be recorded in the logbook.

Change history for the information contained in the annexes may be ‘on demand’, in which case the logbook would indicate the date of the revision of PSMF content and/or Annex update(s), the history of changes for annex content would also be updated. Information that is being regularly updated and is contained in the annexes, such as product and standard operating procedure lists or compliance figures, may include outputs from controlled systems (such as electronic document management systems or regulatory databases). The superseded

versions of such content may be managed outside of the PSMF content itself, provided that the history of changes is maintained and available to the SFDA on request. If the PSMF has not been requested or has remained unchanged for a period of time (for example, if the changes in the content of Annexes are managed outside of the PSMF), it is recommended that a review is conducted periodically. Marketing authorizations holders need to ensure that the obligations concerning the timely provision of the PSMF can be met. It is also noted that the QPPV must be able to gain access to current and accurate information about the pharmacovigilance system, hence permanent access to the PSMF must be enabled, including the information contained in the annexes (either via the pharmacovigilance master file itself or via access to the systems used to generate the annex content).

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

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

The PSMF should be retained in a manner that ensures its legibility and accessibility.

II.B.6. PSMF presentation

The PSMF shall be continuously accessible to the QPPV and to the SFDA on request. The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements. Although provision of the document within 7 days of request by the SFDA, MAHs should be aware that immediate access to the PSMF may also be required by the SFDA, at the stated PSMF location or QPPV site (if different).

II.B.6.1. Format and layout

The PSMF may be in electronic form on condition that a clearly arranged printed copy can be

made available to the SFDA if requested. In any format, the PSMF should be legible, complete, provided in a manner that ensures all documentation is accessible and allow full traceability of changes. Therefore, it may be appropriate to restrict access to the PSMF in order to ensure appropriate control over the content and to assign specific responsibilities for the management of PSMF in terms of change control and archiving.

The PSMF should be written in English, indexed in a manner consistent with the headings described in this Module, and allow easy navigation to the contents. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

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

Cover Page to include:

- The name of the MAH, the MAH of the QPPV responsible for the pharmacovigilance system. described (if different), as well as the relevant third-party company name (if applicable).
- The name of other concerned MAH(s) (sharing the pharmacovigilance system).
- The list of PSMFs for the MAH (concerning products with a different pharmacovigilance system).
- The date of preparation / last update.

The headings used in II.B.4 should be used for the main content of the PSMF. The minimum required content of the annexes is outlined in II.B.4.8, and additional information may be included in the annexes, provided that the requirements for the content of the main sections (II.B.1-7) are also met. The positioning of content in the annexes is further outlined; the bulleted points are descriptions of possible content (and not required headings):

The QPPV, annex A

- The list of tasks that have been delegated by the QPPV, or the applicable procedural document
- The curriculum vitae of the QPPV and associated documents

The Organizational Structure of the MAH, Annex B

- The lists of contracts and agreements

Sources of safety data, Annex C

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

Computerized systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E

- Lists of procedural documents

Pharmacovigilance System Performance, Annex F

- Lists of performance indicators
- Current results of performance assessment in relation to the indicators

Quality System, Annex G

- Audit schedules
- List of audits conducted and completed

Products, Annex H

- List(s) of products covered by the pharmacovigilance system
- Any notes concerning the MAH per product

Document and Record Control, Annex I

- Logbook
- Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself

Documentation to support notifications and signatures concerning the PSMF, as required. Where there is no content for an annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided should still be named according to the format described. For example, Annex E should not be renamed to Annex D in circumstances where no Annex concerning computerized systems and databases is used, Annex D should simply be described as 'unused' in the indexing, in order that recipients of the PSMF are assured that missing content is intended.

II.C. OPERATION WITHIN THE KSA

II.C.1. Responsibilities

II.C.1.1. MAHs and applicants

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

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

The applicant/MAH is responsible for establishing the PSMF in the KSA (at any MAH or contractual partner site including the site of a contractor or marketing partner) and for registering the master file location with the SFDA in the marketing authorization application (as applicable). The PSMF shall describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.

The PSMF creation, maintenance in a current and accessible state (permanently available for audit and inspection purposes) and provision to the SFDA can be outsourced to a third party, but the MAH retains ultimate responsibility for compliance with the legal requirements.

When the QPPV and related contact details change or when the location of the PSMF changes, the MAH is required to submit the appropriate variation application(s) to the SFDA, as applicable. MAHs will also be responsible for notifying the SFDA immediately of any change in the QPPV details and the PSMF address details.

II.C.2. Accessibility of the PSMF

The PSMF shall be maintained in a current state and be permanently available to the QPPV. It shall also be permanently available for inspection, at the site where it is kept (the stated

location), irrespective of whether the inspection has been notified in advance or is unannounced.

The MAH shall maintain and make available on request a copy of the PSMF. The MAH must submit the copy 7 days at the latest after receipt of the request from the SFDA. The PSMF should be submitted in a readable electronic format or clearly arranged printed copy.

In the situation where the same PSMF is used by more than one MAH (where a common pharmacovigilance system is used) the concerned PSMF should be accessible to each, as any of the applicable MAHs shall be able to provide the file to the SFDA within 7 days, upon request.

The PSMF 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.

II.C.3. Special considerations for the multinational MAHs/applicants

The content of the PSMF 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. Despite this fact, pharmacovigilance activities on the national level as described in the PSMF may not be applied to the same extent by all the MAH's national offices/ affiliates, furthermore, some additional national requirements and details may also apply. Accordingly, 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 QPPV, which pharmacovigilance activities are carried out in the KSA, which are carried out in the headquarter/globally and how they integrate together.

For the Multinational MAH/Applicant the following two documents are required to have (for submission requirement see II.C.3.5.):

1. The PSMF (according to European Good Pharmacovigilance Practice which is the base for this guideline) and,
2. National pharmacovigilance sub-system file (national PSSF) which describes the key elements of pharmacovigilance activities in the KSA.

II.C.3.1. The PSMF general consideration

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

II.C.3.2. The information to be contained in the national PSSF

The national pharmacovigilance sub-system file (national PSSF) shall include information and documents to describe the pharmacovigilance sub-system at the national level. 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 QPPV.

The registration and continuous maintenance described in the II.B.2. apply. The control associated with change of content as described in section II.B.5. applies.

II.C.3.2.1. National PSSF section on "QPPV"

Please note that the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

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

The information relating to the QPPV provided in the national PSSF shall include:

- A job description of the QPPV guaranteeing that the QPPV has sufficient authority over the pharmacovigilance activity on the national level in order to promote, maintain and improve compliance with national regulations;
- A summary curriculum vitae with the key information on the role of the QPPV;
- Contact details;
- Details of back-up arrangements to apply in the absence of the QPPV for pharmacovigilance; and
- Checklist on the following required practical experience/ trainings.

Taking into consideration that pharmacovigilance practice and regulations are relatively new in the SFDA, thus having an experienced QPPV may be challenging. Accordingly, it might be acceptable by the SFDA that for only a transitional period the QPPV qualifications may be

expressed in terms of his/her pharmacovigilance training rather than practical experience in pharmacovigilance. Under these circumstances, once the QPPV is appointed, the MAH is responsible of providing him/her the unachieved trainings in light of the checklist below. (Consult with the SFDA for transitional period duration & conditions, if any,).

Topic	Practical experience*
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	
Introduction to pharmaco-epidemiology	
Biostatistics	
Basics of signal detection	
Medical Aspects of Adverse Drug Reactions	
Risk benefit assessment in Pharmacovigilance	
National pharmacovigilance regulations	
PSUR/PBRER overview	
RMP overview	
PSMF overview	
Risk communication, DHPC	

***** during the transitional period: add 3rd column to highlight the trainings the table header will be as follow:

Topic	Practical experience	Training

If applicable, a list of tasks that have been delegated by the QPPV shall also be included in the Annexes (see II.C.3.2.8.). This should outline the preauthorized activities that are delegated and to whom.

The details provided in relation to the QPPV should also include the description of the QPPV qualifications, experience and registrations relevant to pharmacovigilance. The contact details supplied should include name, postal, telephone, fax and e-mail and represent the usual working address of the QPPV.

II.C.3.2.2. National PSSF section on the "organizational structure of the MAH's local office"

Please note that the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

A description of the organizational structure of the MAH's local office relevant to the national pharmacovigilance sub-system must be provided. The description should provide a clear overview of the company(ies) involved, the main pharmacovigilance department and the relationship(s) between organizations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. Specifically, the national PSSF shall describe:

- The organizational structure of the MAH's local office, showing the position of the QPPV in the organization.
- The site(s) where the pharmacovigilance functions on the national level are undertaken covering ICSR collection, evaluation, safety database case entry, PSUR/PBRER production (integration with global system), signal detection and analysis (integration with global system), RMP management, pre- and post-authorization study management, and management of safety.

Diagrams may be particularly useful; the name of the department or third party should be indicated.

Delegated activities

The national PSSF, where applicable, shall contain a description of the preauthorized delegated activities and/or services relating to the fulfilment of pharmacovigilance obligations.

Links with other organizations, such as co-marketing agreements and contracting of pharmacovigilance activities on the national level should be outlined. A description of the

location and nature of contracts and agreements relating to the fulfilment of pharmacovigilance obligations should be provided. This may be in the form of a list/table to show the parties involved, the roles undertaken and the concerned product(s) and territories. The list should be organized according to; service providers (e.g. medical information, auditors, patient support program providers, study data management etc.), commercial arrangements (distributors, licensing partners, co-marketing etc.) and other technical providers (hosting of computer systems etc.). Individual contractual agreements should be annexed with the national PSSF when the latter is submitted. Individual contractual agreements shall be made available at the request of national medicines authorities at any time or during inspection and audit and the list provided in the Annexes (see II.C.3.2.8).

II.C.3.2.3. National PSSF section on the "sources of safety data"

Please note that the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

Description supported by flow diagrams shall be used to indicate the main stages of safety data collection for solicited and spontaneous case collection for products authorized in the SFDA, timeframes and parties involved. However, represented, the description of the process for ICSRs from collection to reporting to national medicines authorities should indicate the departments and/or third parties involved.

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

II.C.3.2.4. National PSSF section on "computerized systems and databases"

Please note that the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

It is understandable that the global safety database for some multinational MAH might be located outside the KSA (at the site where the main pharmacovigilance activities are performed globally e.g. headquarter). However, the QPPV must have online access to local safety cases and all pharmacovigilance data arising from KSA; otherwise, a local database of the local data should always be kept in the local office in Saudi Arabia. In addition, the MAH must periodically reconcile the line listing of received local ICSRs to ensure the completeness of the local database.

The location, functionality and operational responsibility for computerized systems and databases used (on the national level) to receive, collate, record and report safety information and an assessment of their fitness for purpose shall be described in the national PSSF.

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

II.C.3.2.5. National PSSF section on "pharmacovigilance processes"

Please note that the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

An essential element of any pharmacovigilance system is that there are clear written procedures in place. Module I describes the required minimum set of written procedures for

pharmacovigilance.

A description of the procedural documentation available on national level (standard operating procedures, manuals, etc.), the nature of the data held (e.g. the type of case data retained for ICSRs) and an indication of how records are held (e.g. safety database, paper file at site of receipt) should be provided in the national PSSF.

A 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), covering the following aspects shall be included in the national PSSF:

- Continuous monitoring of product benefit-risk profile(s) applied and the result of evaluation and the decision-making process for taking appropriate measures; this should include signal generation, detection and evaluation (in integration with the MAH's headquarter). This may also include several written procedures and instructions concerning safety database outputs, interactions with clinical departments etc.;
- Risk management system(s) and monitoring of the outcome of risk minimization measures; several departments may be involved in this area and interactions should be defined in written procedures or agreements. (in integration with the MAH's headquarter);
- ICSR collection, collation, follow-up, assessment and reporting; the procedures applied to this area should clarify what are local and what are global activities;
- PSUR/PBRER scheduling, production and submission (see Module VII) (in integration with the MAH's headquarter)
- Communication of safety concerns to consumers, healthcare professionals and the national medicines authorities;
- Implementation of safety variations to the SPC and PIL; procedures should cover both internal (within the MAH) and external communications.

In each area, the MAH should be able to provide evidence of a sub-system that supports appropriate and timely decision making and action on the national level (taking into consideration liaising with the MAH's headquarter).

The description must be accompanied by the list of the following processes for compliance management, as well as interfaces with other functions (on the national level and as

appropriate in integration with MAH's headquarter):

1. The continuous monitoring of pharmacovigilance data, the examination of options for risk minimization and prevention and appropriate measures are taken by the MAH;
2. The scientific evaluation by the MAH 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 authorities 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 signals;
5. Effective communication by the MAH with the national medicines authorities, including communication on new risks or changed risks, the PSMF & national PSSF, risk management systems, risk minimization measures, PSUR/PBRERs, corrective and preventive actions, and post-authorization studies;
6. The update of product information by the MAH in the light of scientific knowledge, and on the basis of a continuous monitoring by the MAH of information released by the national medicines authorities;
7. Appropriate communication by the MAH of relevant safety information to healthcare professionals and patients.

These interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to national medicines authority requests for information, literature searching, safety database change control, safety data exchange agreements, safety data archiving, pharmacovigilance auditing, quality control and training. The list, which may be located in the Annexes, should comprise in cross matching with each one of the topics highlighted above in this section, the topic name, the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.). Procedures belonging to service providers and other third parties should be clearly identified. In addition, any specific local (in the SFDA) procedures should be also indicated.

II.C.3.2.6. National PSSF section on "pharmacovigilance sub-system performance"

Please note that the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

The national PSSF should contain evidence of the ongoing monitoring of performance of the national pharmacovigilance sub-system including compliance of the main outputs of pharmacovigilance. The national PSSF should include a description of the monitoring methods applied and contain as a minimum (the following should focus on performance on the national level):

- An explanation of how the reporting of domestic ICSRs is assessed. In the annex, figures/graphs should be provided to show the timeliness of 15-day and 90-day reporting (to national medicines authority) over the past year;
- A description of any metrics used to monitor the quality of submissions and performance of pharmacovigilance. This should include information provided by national medicines authorities regarding the quality of ICSR reporting, PSUR/PBRERs or other submissions;
- An overview of the timeliness of PSUR/PBRER reporting to the SFDA (the annex should reflect the latest figures used by the MAH to assess compliance on national level);
- An overview of the methods used to ensure timeliness of safety variation submissions compared to internal and national medicines authority deadlines, including the tracking of required safety variations that have been identified but not yet been submitted;
- Where applicable, an overview of adherence to National Display of RMP commitments, or other obligations or conditions of marketing authorization(s) relevant to pharmacovigilance.

Targets for the performance of the pharmacovigilance sub-system shall be described and explained. A list of performance indicators must be provided in the Annex to the national PSSF, alongside the results of (actual) performance measurements.

II.C.3.2.7. National PSSF section on "quality system"

Please note that the information provided in this section of the national PSSF shall focus on the national pharmacovigilance sub-system

A description of the quality management system should be provided, in terms of the structure of the organization and the application of the quality to pharmacovigilance.

This shall include:

Document and Record Control

Provide a description of the archiving arrangements (on national level) for electronic and/or hardcopy versions of the different types of records and documents for pharmacovigilance and quality system (see also Module I).

Procedural documents

A general description of the types of documents used in pharmacovigilance (standards, operating procedures, work instructions etc.), the applicability of the various documents at local level within the organization, and the controls that are applied to their accessibility, implementation and maintenance.

Information about the documentation systems applied to relevant procedural documents under the control of third parties.

A list of specific procedures and processes related to the pharmacovigilance activities (on the national level) and interfaces with other functions, with details of how the procedures can be accessed must be provided, and the detailed guidance for the inclusion of these is in section II.C.3.2.5.

Training

Staff should be appropriately trained for performing pharmacovigilance related activities and this includes not only staff within pharmacovigilance departments but also any individual that may receive safety reports such as sales personnel or clinical research staff.

A description of the resource management for the performance of pharmacovigilance activities on the national level:

The organizational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organizational structure (see II.C.3.2.3.)

Information about sites where the personnel are located (this is described under sections II.C.3.2.2.) whereby the sites are provided in the national PSSF in relation to the organization of specific pharmacovigilance activities. However, a description should be provided in order

to explain the training organization in relation to the personnel and site information;

A summary description of the training concept, including a reference to the location training files, record as well as the trainings materials.

Auditing

Information about quality assurance auditing of the national pharmacovigilance sub-system should be included in the national PSSF. A description of the approach used to plan audits of the national pharmacovigilance sub-system and the reporting mechanism and timelines should be provided, with a current list of the scheduled and completed audits concerning the national pharmacovigilance sub-system maintained in the annex referred to II.C.3.2.8. This list should describe the date(s) (of conduct and of report), scope and completion status of audits of service providers, specific pharmacovigilance activities or sites undertaking pharmacovigilance and their operational interfaces relevant to the fulfilment of the pharmacovigilance obligations and cover a rolling 5-year period.

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

As a means of managing the national pharmacovigilance sub-system, and providing a basis for audit or inspection, the national PSSF should also describe the process for recording, managing and resolving deviations from the quality system. The national PSSF shall also

document deviations from pharmacovigilance procedures on the national level, their impact and management until resolved. This may be documented in the form of a list referencing a deviation report, and its date and procedure concerned.

II.C.3.2.8. Annex to the national PSSF

Please note that the information/documents provided in this annex of the national PSSF shall focus on the national pharmacovigilance sub-system

An annex to the national PSSF shall contain the following documents:

- A list of medicinal products covered by this national PSSF in the KSA, the following should be provided for each medicinal product in the list:
  - the name of the medicinal product,
  - the name of the active substance(s),
  - the authorization number in the KSA,
  - the presence on the market in the KSA (i.e. marketing status),
  - other country (ies) in which this product is authorized,
  - the presence on the market in these other country(ies) stated in the list (i.e. marketing status),

The list should be organized per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimization measures contained in the RMP or laid down as conditions of the marketing authorization, non-standard PSUR/PBRER periodicity. The monitoring information may be provided as a secondary list.

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

Where national pharmacovigilance sub-systems are shared, all products that utilize the national pharmacovigilance sub-system should be included, so that the entire list of products covered by the file is available. The products lists may be presented separately, organized per

MAH. Alternatively, a single list may be used, which is supplemented with the name of the MAH(s) for each product, or a separate note can be included to describe the product(s) and the MAH(s) covered;

- A list of written policies and procedures for the compliance management (see II.C.3.2.5.);
- A list of contractual agreements covering delegated activities in the KSA including the medicinal products. In addition, a copy of the individual contractual agreements shall also be included in this annex when the PSMF is submitted to the national medicines authorities;
- A list of tasks that have been delegated by the QPPV (if any);
- A list of all completed audits on the national level, for a period of five years, and a list of audit schedules on the national level;
- Where applicable, a list of performance indicators;
- Where applicable, a list of other national PSSF(s) held by the same MAH. This list should include the national PSSF number(s), the name of MAH and the name of the QPPV responsible for the pharmacovigilance sub-system used. If the pharmacovigilance system is managed by another party that is not a MAH, the name of the service provider should also be included.
- A logbook of any change of the content of the national PSSF made within the last five years except the changes in annexes and the following QPPV information: CV, contact details, back-up arrangements and contact person for pharmacovigilance on the national level. In addition, other change control documentation should be included as appropriate. Documented changes shall include at least the date, person responsible for the change and the nature of the change.

II.C.3.3. National PSSF presentation

The National PSSF shall be continuously accessible to the QPPV and to the national medicines authorities any time on request. The information shall be succinct, accurate and reflect the current system in place, which means that whatever format is used, it must be possible to keep the information up to date and, when necessary, to revise to take account of experience gained, technical and scientific progress and amendments to the legislative requirements. Although provision of the document within 7 days of request by a national

medicines authority is required, MAHs should be aware that immediate access to the National PSSF may also be required by the national medicines authorities.

II.C.3.3.1. Format and layout

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

The national PSSF should be written in English, indexed in a manner consistent with the headings described in this Module, and allow easy navigation to the contents with. In general, embedded documents are discouraged. The use of electronic book-marking and searchable text is recommended. Documents such as copies of signed statements or agreements should be included as appendices and described in the index.

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

Cover Page to include:

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

The headings used in II.C.3.2. Should be used for the main content of the national PSSF. The minimum required content of the Annexes is outlined in II.C.3.2.8., and additional

information may be included in the Annexes, provided that the requirements for the content of the main sections (II.C.3.2.1-7) are also met. The positioning of content in the Annexes is further outlined; the bulleted points are descriptions of possible content (and not required headings):

The QPPV for national pharmacovigilance sub-system, Annex A

- The list of tasks that have been delegated by the QPPV (if any), or the applicable procedural document
- The curriculum vitae of the QPPV and associated documents
- Contact details

The Organizational Structure of the MAH, Annex B

- The lists of contracts and agreements
- a copy of the individual contractual agreements relevant to the KSA

Sources of safety data, Annex C

Computerized systems and Databases, Annex D

Pharmacovigilance Process, and written procedures, Annex E

- Lists of procedural documents

Pharmacovigilance Sub-System Performance, Annex F

- Lists of performance indicators
- Current results of performance assessment in relation to the indicators

Quality System, Annex G

- Audit schedules (for national pharmacovigilance sub-system)
- List of audits conducted and completed (for national pharmacovigilance sub-system)

Products, Annex H

- List(s) of products covered by the national pharmacovigilance sub-system described in this national PSSF
- Any notes concerning the MAH per product

Document and Record Control, Annex I

- Logbook
- Documentation of history of changes for Annex contents, indexed according to the Annexes A-H and their content if not provided within the relevant annex itself

Documentation to support notifications and signatures concerning the national PSSF, as required. Where there is no content for an Annex, there is no need to provide blank content pages with headings, however, the Annexes that are provided should still be named according to the format described. For example, Annex E should **NOT** be renamed to Annex D in circumstances where no Annex concerning computerized systems and databases is used, Annex D should simply be described as 'unused' in the indexing, in order that recipients of the PSMF are assured that missing content is intended.

II.C.3.4. Summary of the applicant's national pharmacovigilance sub-system

Except in the situations described in see II.C.3.5.1. where the full PSSF (along together with its summary) is requested to be submitted in the marketing authorization application; only a summary of the applicant's national pharmacovigilance sub-system is required to be included in the marketing authorization application, which shall include the following elements in module 1.6. of the dossier:

- proof that the applicant has at his disposal a QPPV and that he resides in the KSA;
- the contact details of the QPPV;
- 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;
- a reference to the location where the national PSSF for the medicinal product is kept.

The national PPSF should not routinely be submitted during the assessment of new marketing authorization applications (i.e. pre-authorization), but may be requested on an ad hoc basis, (see II.C.3.5. for submission requirement).

II.C.3.5. Submission of multinational MAH's PSMF and national PSSF

The PSMF and the national PSSF shall be maintained in a current state and be permanently

available to be submitted.

II.C.3.5.1. In the marketing authorization application:

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

- The applicant has not previously held a marketing authorization in the KSA, full PSMF and the national PSSF are appropriate to review the description of a pharmacovigilance system;
- The applicant has not previously submitted the PSMF and the national PSSF in the KSA or is in the process of establishing a new pharmacovigilance system;
- The applicant had major changes in its organization, such as mergers and acquisitions or in its pharmacovigilance system
- the applicant has major or critical findings in the previous assessment of the pharmacovigilance system (global &/or local) by the national medicines authority;
- 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 and national PSSF, if the MAH has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorization pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorization is granted (see module III);
- Where specific concerns about the pharmacovigilance system (global &/or local) and/or the product safety profile exist;
- Any other situation as seen appropriate by the national medicines authority;

In case that these situations apply to the national PSSF but not the PSMF; then the multinational MAH can submit the "summary of PSMF" & the "national PSSF", and vice versa.

Except in the above situations, the PSMF and/or the national PSSF (as appropriate) 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.

Table II.1 Conditions to submit the PSMF and the national PSSF

Conditions	Document submitted
Situations in II.C.3.5.1 apply to both PSMF and the national PSSF	PSMF & National PSSF
Situations in II.C.3.5.1 apply to only national PSSF	Summary PSMF & National PSSF
Situations in II.C.3.5.1 apply to only PSMF	PSMF & summary of national PSSF
Situations in II.C.3.5.1 do NOT apply to both PSMF and the national PSSF	Summary PSMF & summary National PSSF

Annex 1

Maintenance

1. The MAH shall keep the PSMF up to date and, where necessary, revise it to take account of experience gained
2. The PSMF and its Annex shall be subject to version control and shall indicate the date when it was last updated by the MAH.
3. Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the PSMF until resolved.
4. The MAH shall notify immediately the SFDA of any change in the location of the PSMF or changes to the contact details and name of the QPPV.

Content of the Annex to the PSMF

The PSMF shall have an Annex containing the following documents:

1. a list of medicinal products covered by the PSMF, including the name of the medicinal product, the international non-proprietary name (INN) of the active substance(s), and the country (s) in which the authorization is valid;
2. a list of written policies and procedures;
3. the list of subcontracts;
4. a list of the tasks that have been delegated by the QPPV;
5. a list of all scheduled and completed audits;
6. where applicable, a list of the performance indicators;
7. where applicable, a list of other PSMFs held by the same MAH;
8. a logbook containing all relevant information.

MODULE III – PHARMACOVIGILANCE INSPECTIONS

III.A. INTRODUCTION

This Module contains guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in the KSA and outlines the role of the different parties involved. General guidance is provided under III.B., while III.C. covers the overall operation of pharmacovigilance inspections in the KSA.

In order to determine that MAHs comply with pharmacovigilance obligations in the KSA, and to facilitate compliance, the SFDA shall conduct pharmacovigilance inspections of MAHs or any firms employed to fulfil MAH's pharmacovigilance obligations. Such inspections shall be conducted by inspectors appointed by the SFDA and empowered to inspect the premises, records, documents and PSMF of the MAH or any firms employed by the MAH to perform the activities including third party organizations. In particular, MAHs are required to provide, on request, the PSMF, which will be used to inform inspection conduct (see Module II).

The objectives of pharmacovigilance inspections are:

- To determine that the MAH has personnel, systems and facilities in place to meet their pharmacovigilance obligations;
- To identify, record and address non-compliance, which may pose a risk to public health;
- To use the inspection results as a basis for enforcement action, where considered necessary.

For MAHs of products, it is the responsibility of the SFDA to ensure that the MAH for the medicinal product satisfies the pharmacovigilance requirements. The PSMF shall be located either where the main pharmacovigilance activities of the MAH are performed or where the QPPV operates. The SFDA may conduct pre-authorization inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system.

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

Any non-compliance should also be rectified by the MAH in a timely manner through the

implementation of a corrective and preventive action plan.

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

III.B. STRUCTURES AND PROCESSES

III.B.1. Inspection types

III.B.1.1. System and product-related inspections

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

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

III.B.1.2. Routine and “for cause” pharmacovigilance inspections

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programs. There is no specific trigger to initiate these inspections, although a risk-based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections, but one or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance. Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

For cause, pharmacovigilance inspections are undertaken when a trigger is recognized, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. For cause inspections may arise when, for example, one or more of the listed below are identified:

- Benefit-risk balance of the product:
  - Change in the benefit-risk balance where further examination through an inspection is considered appropriate;
  - Delays or failure to identify or communicate a risk or a change in the benefit-risk balance;
  - Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the SFDA, as applicable;
  - Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by the SFDA;
  - Suspension or product withdrawal with no advance notice to the SFDA;
- Reporting obligations (expedited and periodic):
  - Delays or omissions in reporting;
  - Poor quality or incomplete reports;
  - Inconsistencies between reports and other information sources;
- Requests from the SFDA:
  - Failure to provide the requested information or data within the deadline specified by the SFDA;
  - Poor quality or inadequate provision of data to fulfil requests for information from the SFDA;
- Fulfilment of commitments:
  - Concerns about the status or fulfilment of RMP commitments;
  - Delays or failure to perform specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization;
  - Poor quality of reports requested as specific obligations;
- Inspections
  - Delays in the implementation or inappropriate implementation of corrective and preventive actions;
  - Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP);

- Inspection information received from other international authorities, which may highlight issues of non-compliance;

- Others:
  - Concerns following review of the PSMF;
  - Non-inspection related information received from other authorities, which may highlight issues of non-compliance;
  - Other sources of information or complaints.

III.B.1.3. Pre-authorization inspections

Pre-authorization pharmacovigilance inspections are inspections performed before a marketing authorization is granted. These inspections are conducted with the intent of examining the existing or proposed pharmacovigilance system as it has been described by the applicant in support of the marketing authorization application. Pre-authorization inspections are not mandatory but may be requested in specific circumstances. Principles and procedures for requesting pre-authorization inspections should be developed to avoid performing unnecessary inspections which may delay the granting of a marketing authorization. The following aspects shall be considered during the validation phase and/or early during the assessment phase:

- The applicant has not previously operated a pharmacovigilance system in the KSA or is in the process of establishing a new pharmacovigilance system;
- Previous information (e.g. inspection history and non-compliance notifications or information from other authorities) indicates that the applicant has a poor history or culture of compliance. If the MAH has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorization pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorization is granted;
- Due to product-specific safety concerns, it may be considered appropriate to examine the applicant's ability:
  - To implement product specific risk-minimization activities; or
  - To meet specific safety conditions which may be imposed; or

- To manage routine pharmacovigilance for the product of concern (e.g. anticipated significant increase in adverse reaction reports when compared to previous products).

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

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

- Non approval of the marketing authorization;
- A re-inspection prior to approval of the marketing authorization to confirm that critical findings and recommendations have been addressed;
- Granting of the marketing authorization with the recommendation to perform an early post-authorization pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the SFDA routine program of pharmacovigilance inspections (see III.B.2.);
- Imposition of safety conditions to the marketing authorization.

III.B.1.4. Post-authorization inspections

Post-authorization pharmacovigilance inspections are inspections performed after a marketing authorization is granted and are intended to examine whether the MAH complies with its pharmacovigilance obligations. They can be any of the types mentioned under III.B.1.1 and IIIB.1.2.

III.B.1.5. Announced and unannounced inspections

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

III.B.1.6. Re-inspections

A re-inspection may be conducted on a routine basis as part of a routine inspection program.

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

III.B.1.7. Remote inspections

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

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

III.B.2. Inspection planning

Pharmacovigilance inspection planning should be based on a systematic and risk-based approach to make the best use of surveillance and enforcement resources whilst maintaining a high level of public health protection. A risk-based approach to inspection planning will enable the frequency, scope and breadth of inspections to be determined accordingly.

In order to ensure that inspection resources are used in an efficient way, the scheduling and conduct of inspections will be driven by the preparation of inspection programs. Sharing of

information and communication between inspectors and assessors is important to ensure successful prioritization and targeting of these inspections.

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

- Inspection related:
  - Compliance history identified during previous pharmacovigilance inspections or other types of inspections (GCP, GMP, GLP and GDP);
  - Re-inspection date recommended by the inspectors or assessors as a result of a previous inspection;
- Product related:
  - Product with additional pharmacovigilance activities or risk-minimization activities;
  - Authorization with conditions associated with safety, e.g. requirement for post-authorization safety studies (PASS) or designation for additional monitoring;
  - Product(s) with large sales volume, i.e. products associated with large patient exposure in the KSA;
  - Product(s) with limited alternative in the market place;
- MAH related:
  - MAH that has never been subject to a pharmacovigilance inspection;
  - MAH with many products on the market in the KSA;
  - Resources available to the MAH for the pharmacovigilance activities they undertake;
  - MAH with no previous marketing authorizations in the KSA;
  - Negative information and/or safety concerns raised by the SFDA, other bodies outside the KSA (i.e. GCP, GMP, GLP and GDP);
  - Changes in the MAH organization, such as mergers and acquisitions;
- Pharmacovigilance system related:
  - MAH with sub-contracted pharmacovigilance activities and/or multiple firms employed to perform pharmacovigilance activities;
  - Change of QPPV since the last inspection;
  - Changes to the pharmacovigilance safety database(s), which could include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data;

- Changes in contractual arrangements with pharmacovigilance service providers or the sites at which pharmacovigilance is conducted;
- Delegation or transfer of PSMF management.

The SFDA may solicit information from MAHs for risk-based inspection planning purposes if it is not readily available elsewhere.

III.B.3. Sites to be inspected

Any party performing pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the MAH may be inspected, in order to confirm their capability to support the MAH's compliance with pharmacovigilance obligations.

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

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

III.B.4. Inspection scope

The inspection scope will depend on the objectives of the inspection as well as the coverage of any previous inspections by the SFDA and whether it is a system or product-related inspection (a description of the types of inspection, inspection triggers and points to consider for the different types of inspection is provided in III.B.1.).

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

- Information supplied in the PSMF;
- Information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the SFDA such as the NPC reporting and data quality audits;

- Specific triggers (see III.B.1.2. for examples of triggers);

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

III.B.4.1. Routine pharmacovigilance inspections

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

- ICSRs:
  - Collecting, receiving and exchanging reports -from all types of sources, sites and departments within the pharmacovigilance system, including from those firms employed to fulfil MAH's pharmacovigilance obligations and departments other than drug safety;
  - Assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality. In addition to examples of ICSRs from the KSA, examples of ICSRs reported from outside the KSA should be examined as part of this review (if applicable);
  - Follow-up and outcome recording, for example final outcome of cases of exposure in pregnancy and medical confirmation of consumer reported events;
  - Reporting according to the requirements for various types of reported ICSRs, including onward reporting to the relevant bodies and timeliness of such reporting;
  - Record keeping and archiving for ICSRs;
- PSUR/PBRERs (as applicable):
  - Completeness and accuracy of the data included, appropriateness of decisions concerning data that are not included;
  - Addressing safety topics, providing relevant analyses and actions;
  - Formatting according to requirements;
  - Timeliness of submissions;
- Ongoing safety evaluation;
  - Use of all relevant sources of information for signal detection;

- Appropriately applied methodology concerning analysis;
- Appropriateness of investigations and follow-up actions, e.g. the implementation of recommendations following data review;
- Implementation of the RMP, or other commitments, e.g. conditions of marketing authorization;
- Timely identification and provision of complete and accurate data to the SFDA, in particular in response to specific requests for data;
- Implementation of approved changes to safety communications and product information, including internal distribution and external publication;

- Interventional (where appropriate) and non-interventional clinical trials:
  - Reporting suspected unexpected serious adverse reactions (SUSARs) and non-interventional study cases;
  - Receiving, recording and assessing cases from interventional and non-interventional trials (see ICSRs);
  - Submission of study results and relevant safety information (e.g. development safety update reports (DSURs) and information included in PSUR/PBRERs), where applicable, PASS or post-authorization efficacy studies (PAES) submissions, particularly when associated with specific obligations or RMP commitments;
  - Appropriate selection of reference safety information, maintenance of investigator brochures and patient information with respect to safety;
  - The inclusion of study data in ongoing safety evaluation;
- Pharmacovigilance system:
  - QPPV roles and responsibilities, e.g. access to the quality system, the PSMF, performance metrics, audit and inspection reports, and their ability to act to improve compliance;
  - The roles and responsibilities of the MAH in relation to the pharmacovigilance system;
  - Accuracy, completeness and maintenance of the PSMF;
  - Quality and adequacy of training, qualifications and experience of staff;

- Coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
- Fitness for purpose of computerized systems;
- Contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance and are adhered to.

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

III.B.4.2. For cause inspections

The scope of the inspection will depend on the specific trigger(s). Some, but not all of the elements listed in III.B.4.1 and below, may be relevant:

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

III.B.4.3. Re-inspections

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

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

The scope of re-inspection will depend on inspection history. It may be appropriate to conduct a complete system review, for example if a long time has elapsed since the previous inspection, in which case the elements listed in III.B.4.1. may be considered for the inspection scope, as appropriate.

III.B.5. Inspection process

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

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

- Sharing of information;
- Inspection planning;
- Pre-authorization inspections;
- Coordination of pharmacovigilance inspections in the KSA;
- Coordination of other countries inspections (including inspections of contractors in other countries);
- Preparation of pharmacovigilance inspections;
- Conduct of pharmacovigilance inspections;
- Reporting of pharmacovigilance inspections and inspection follow-up;
- Communication and prioritization of pharmacovigilance inspections and findings;
- Interaction with SFDA in relation to inspections and their follow-up;
- Record-keeping and archiving of documents obtained or resulting from pharmacovigilance inspections;
- Unannounced inspections;
- Sanctions and enforcement in case of serious non-compliance;
- Recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

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

III.B.6. Inspection follow-up

When non-compliance with pharmacovigilance obligations is identified during an inspection, follow-up will be required until a corrective and preventive action plan is completed. The following follow-up actions should be considered, as appropriate:

- Review of the MAH's corrective and preventive action plan;

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

Sharing information and communication between inspectors and assessors is important for the proper follow-up of inspections.

III.B.7. Regulatory actions and sanctions

Under the KSA legislation, in order to protect public health, the SFDA are obliged to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance obligations is detected, the necessary action will be judged on a case-by-case basis. What action is taken will depend on the potential negative impact of non-compliance(s) on public health, but any instance of non-compliance may be considered for enforcement action. Action may be taken by the SFDA as appropriate. The SFDA shall take the necessary measures to ensure that a MAH is subject to effective, proportionate and dissuasive penalties.

In the event of non-compliance, possible regulatory options include the following, in accordance with guidance and, as applicable, rules set in legislation:

- Education and facilitation: the SFDA may communicate with MAH representatives (e.g. in a meeting) to summarize the identified non-compliances, to clarify the legal

requirements and the expectations of the regulator, and to review the MAH's proposals for corrective and preventive actions;

- Inspection: non-compliant MAHs may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- Warning letter, non-compliance statement or infringement notice: these are non-statutory or statutory instruments in accordance with national legislation which SFDA may issue stating the legislation and guideline that has been breached, reminding MAHs of their pharmacovigilance obligations or specifying the steps that the MAH must take and in what timeframe in order to rectify the noncompliance and in order to prevent a further case of non-compliance;
- The SFDA may consider making public a list of MAHs found to be seriously or persistently non-compliant;
- Actions against a marketing authorization(s) or authorization application(s) e.g.
  - Urgent safety restriction;
  - Variation of the marketing authorization;
  - Suspension or revocation of the marketing authorization;
  - Delays in approvals of new marketing authorization applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorizations;
  - Requests for pre-authorization inspections;
- Product recalls e.g. where important safety warnings have been omitted from product information;
- Action relating to marketing or advertising information;
- Amendments or suspension of clinical trials due to product-specific safety issues;
- Administrative penalties, usually fixed fines or based on company profits or levied on a daily basis;
- Referral for criminal prosecution with the possibility of imprisonment (in accordance with national legislation).

III.B.8. Record management and archiving

The principles and requirements to be followed according to the SFDA procedure on Record

Keeping and Archiving of Documents Obtained or Resulting from the Pharmacovigilance Inspections.

III.B.9. Qualification and training of inspectors

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

It is recommended that inspectors are appointed based upon their experience and the minimum requirements defined by the SFDA.

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

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

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

III.B.10. Quality management of pharmacovigilance inspection process

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

III.C. OPERATION OF PHARMACOVIGILANCE INSPECTIONS IN THE KSA

III.C.1. Inspection programs

A program for routine inspections for authorized products will be determined by the SFDA.

These inspections will be prioritized based on the potential risk to public health. If the same pharmacovigilance system is used for a variety of authorization types, then the results of the SFDA inspection may be applicable for all products covered by that system.

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

The SFDA is also responsible for the planning and coordination of pharmacovigilance inspections in order to ensure compliance with the legislation and to verify the effectiveness of the MAH's pharmacovigilance system.

Based on the information from other inspections, the SFDA will prioritize the inspections in its program and will use the information for the preparation of an appropriate scope for the inspection. For example, the SFDA may seek to verify the fulfilment of requirements concerning the implementation of specific risk-minimization measures, communications concerning safety, locally conducted safety studies, or issues linked to healthcare systems. A broader examination of pharmacovigilance applied to particular products of interest may also be appropriate if this was not covered within the scope of a supervisory authority inspection.

III.C.2. Role of the MAHs and applicants

MAHs with authorized products and applicants who have submitted new applications subject to pharmacovigilance inspections (see III.B.1). Therefore, both have responsibilities in relation to inspections, including but not limited to the following:

- Always to be inspection-ready as inspections may be unannounced;
- To maintain and make available to the inspectors on request, no later than 7 calendar days after the receipt of a request, the PSMF;
- To ensure that the sites selected for inspection, which may include firms employed by the MAH to perform pharmacovigilance activities, agree to be inspected before the inspection is performed;
- To make available to the inspectors any information and/or documentation required for the preparation of the inspection within the deadline given or during the conduct of the inspection;

- To ensure that relevant staff involved in pharmacovigilance activities or related activities are present and available during the inspection for interviews or clarification of issues identified;
- To ensure that relevant pharmacovigilance data is accessible;
- To ensure that appropriate and timely corrective and preventive action plans are implemented to address findings observed during an inspection, with appropriate prioritization of critical and/or major findings.

MODULE IV – PHARMACOVIGILANCE AUDITS

IV.A. INTRODUCTION

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

This Module provides guidance on planning and conducting the legally required audits, the role, context and management of pharmacovigilance audit activity. This Module 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 Module are aligned with internationally accepted auditing standards, issued by relevant international auditing standardization organizations (the Institute of Internal Auditors; the International Organization for Standardisation (ISO); the Information Systems Audit and Control Association (ISACA); the International Auditing and Assurance Standards Board (IAASB); the International Organization of Supreme Audit Institutions (INTOSAI) and the Committee of Sponsoring Organizations (COSO)) and support a risk-based approach to pharmacovigilance audits.

Section IV.B. outlines the general structures and processes that should be followed to identify the most appropriate pharmacovigilance audit engagements and describes the steps which can be undertaken by MAHs or the SFDA, to plan, conduct and report upon an individual pharmacovigilance audit engagement. This section also provides an outline of the general quality system and record management practices for pharmacovigilance audit processes.

IV.A.1. Terminology

Audit, Audit findings, Audit plan, Audit program, Audit recommendations,

Auditee: [entity] being audited (ISO 19011 (3.7)). (The Institute of Internal Auditors)

Compliance: Conformity and adherence to policies, plans, procedures, laws, regulations, contracts, or other requirements (IIA International Standards for the Professional Practice of Internal Auditing).

Control(s): Any action taken by management and other parties to manage risk and increase the likelihood that established objectives and goals will be achieved. Management plans,

organizes, and directs the performance of sufficient actions to provide reasonable assurance that objectives and goals will be achieved (IIA International Standards for the Professional Practice of Internal Auditing).

Evaluation (of audit activities): Professional auditing bodies promote compliance with standards, including in quality assurance of their own activities, and codes of conduct, which can be used to address adequate fulfilment of the organization's basic expectations of Internal Audit activity and its conformity to internationally accepted auditing standards.

Finding(s): see Audit findings

Auditors' independence: The freedom from conditions that threaten objectivity or the appearance of objectivity. Such threats to objectivity must be managed at the individual auditor, engagement, functional and organizational levels. (IIA International Standards for the Professional Practice of Internal Auditing).

Internal Control: Internal control is an integral process that is effected by an entity's management and personnel and is designed to address risk and provide reasonable assurance that in pursuit of the entity's mission, the following general objectives are being achieved: executing orderly, ethical, economical, efficient and effective operations, fulfilling accountability obligations, complying with applicable laws and regulations and safeguarding resources against loss, misuse and damage (for further information refer to the Committee of Sponsoring Organizations (COSO) standards).

Auditors' objectivity: An unbiased mental attitude that allows internal auditors to perform engagements in such a manner that they have an honest belief in their work product and that no significant quality compromises are made. Objectivity requires internal auditors not to subordinate their judgment on audit matters to that of others. (IIA International Standards for the Professional Practice of Internal Auditing)

IV.B. STRUCTURES AND PROCESSES

IV.B.1. Pharmacovigilance audit and its objective

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

In general, an audit is a systematic, disciplined, independent and documented process for

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

IV.B.2. The risk-based approach to pharmacovigilance audits

A risk-based approach is one that uses techniques to determine the areas of risk, where risk is defined as the probability of an event occurring that will have an impact on the achievement of objectives, taking account of the severity of its outcome and/or likelihood of non-detection by other methods. The risk-based approach to audits focuses on the areas of highest risk to the organization's pharmacovigilance system, including its quality system for pharmacovigilance activities. In the context of pharmacovigilance, the risk to public health is of prime importance. Risk can be assessed at the following stages:

- Strategic level audit planning resulting in an audit strategy (long term approach), which should be endorsed by upper management;
- Tactical level audit planning resulting in an audit program, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that program; and
- Operational level audit planning resulting in an audit plan for individual audit engagements, prioritizing audit tasks based on risk and utilizing risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system [see IV.B.2.3.1.].

Risk assessment should be documented appropriately for the strategic, tactical and operational planning of pharmacovigilance audit activity in the organization (see IV.B.2.1., IV.B.2.2. and IV.B.2.3. respectively).

IV.B.2.1. Strategic level audit planning

The audit strategy is a high-level statement of how the audit activities will be delivered over a period of time, longer than the annual program, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit program is based.

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

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

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

- Changes to legislation and guidance;
- Major re-organization or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically for MAHs, this may lead to a significant increase in the number of products for which the system is used);
- Change in key managerial function(s);
- Risk to availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, re-organization, increase in volumes of work;
- Significant changes to the system since the time of a previous audit, e.g. introduction of a new database(s) for pharmacovigilance activities or of a significant upgrade to the existing database(s), changes to processes and activities in order to address new or amended regulatory requirements;
- First medicinal product on the market (for a MAH);
- Medicinal product(s) on the market with specific risk minimization measures or other specific safety conditions such as requirements for additional monitoring;

- Criticality of the process, e.g.:
  - For the SFDA: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;
  - For MAHs: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the MAH should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the MAH, in addition to considering the other factors included in this list;
- Outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritized depending on criticality); if the area/process has previously been audited, the audit findings are a factor to consider when deciding when to re-audit the area/process, including the implementation of agreed actions;
- Identified procedural gaps relating to specific areas/processes;
- Other organisational changes that could negatively impact on the area/process, e.g. if a change occurs to a support function (such as information technology support) this could negatively impact upon pharmacovigilance activities.

IV.B.2.2. Tactical level audit planning

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

The risk-based audit program should be based on an appropriate risk assessment and should focus on:

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

The risk-based audit program should also consider historical areas with insufficient past audit

coverage, and high-risk areas identified by and/or specific requests from management and/or persons responsible for pharmacovigilance activities.

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

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

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

IV.B.2.3. Operational level audit planning and reporting

IV.B.2.3.1. Planning and fieldwork

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

Individual pharmacovigilance audits should be undertaken in line with the approved risk-based audit program (see IV.B.2.2.). When planning individual audits, the auditor identifies and assesses the risks relevant to the area under review and employs the most appropriate risk-based sampling and testing methods, documenting the audit approach in an audit plan.

IV.B.2.3.2. Reporting

The findings of the auditors should be documented in an audit report and should be communicated to management in a timely manner. The audit process should include mechanisms for communicating the audit findings to the auditee and receiving feedback and reporting the audit findings to management and relevant parties, including those responsible for pharmacovigilance systems, in accordance with legal requirements and guidance on pharmacovigilance audits. Audit findings should be reported in line with their relative risk level and should be graded in order to indicate their relative criticality to risks impacting the pharmacovigilance system, processes and parts of processes. The grading system should be defined in the description of the quality system for pharmacovigilance and should take into

consideration the thresholds noted below which would be used in further reporting under the legislation as set out in section IV.C.2:

- **Critical** is a fundamental weakness in one or more pharmacovigilance processes or practices that adversely affects the whole pharmacovigilance system and/or the rights, safety or well-being of patients, or that poses a potential risk to public health and/or represents a serious violation of applicable regulatory requirements.
- **Major** is a significant weakness in one or more pharmacovigilance processes or practices, or a fundamental weakness in part of one or more pharmacovigilance processes or practices that is detrimental to the whole process and/or could potentially adversely affect the rights, safety or well-being of patients and/or could potentially pose a risk to public health and/or represents a violation of applicable regulatory requirements which is however not considered serious.
- **Minor** is a weakness in the part of one or more pharmacovigilance processes or practices that is not expected to adversely affect the whole pharmacovigilance system or process and/or the rights, safety or well-being of patients.

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

IV.B.2.4. Actions based on audit outcomes and follow-up of audits

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

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

Upper management and those charged with governance, should ensure that effective action is

implemented to address the audit findings. The implementation of agreed actions should be monitored in a systematic way, and the progress of implementation should be communicated on a periodic basis proportionate to the planned actions to upper management.

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

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

IV.B.3. Quality system and record management practices

IV.B.3.1. Competence of auditors and quality management of audit activities

IV.B.3.1.1. Independence and objectivity of audit work and auditors

The organization should assign the specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities should be independent. The organization's management should ensure this independence and objectivity in a structured manner and document this.

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

IV.B.3.1.2. Qualifications, skills and experience of auditors and continuing professional development

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

knowledge, skills and abilities in:

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

IV.B.3.1.3. Evaluation of the quality of audit activities

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

IV.B.3.2. Audits undertaken by outsourced audit service providers

Ultimate responsibility for the operation and effectiveness of the pharmacovigilance system resides within the organization (i.e. MAH). Where the organization decides to use an outsourced audit service provider to implement the pharmacovigilance audit requirements on the basis of this GVP module and perform pharmacovigilance audits:

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

IV.B.3.3. Retention of audit reports

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

IV.C. PHARMACOVIGILANCE AUDIT POLICY FRAMEWORK AND ORGANIZATIONAL STRUCTURE

IV.C.1. MAHs in the KSA

IV.C.1.1. Requirement to perform an audit

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

See IV.C.2. for further details of the requirements for audit reporting by the MAH.

IV.C.1.1.1. The qualified person responsible for pharmacovigilance in the KSA (QPPV)

The responsibilities of the QPPV in respect of audit are provided in Module I. Furthermore, the QPPV 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.

The QPPV should be notified of any audit findings relevant to the pharmacovigilance system in the KSA, irrespective of where the audit was conducted.

IV.C.2. Requirements for audit reporting in the KSA

IV.C.2.1. Reporting by the MAH

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

The MAHs should ensure that a list of all scheduled and completed audits is kept in the annex to the PSMF and that they comply with reporting commitments in line with the legislation, GVP guidance and their internal reporting policies. The dates and results of audits and follow-up audits shall be documented.

IV.C.3. Confidentiality

Documents and information collected by the internal auditor should be treated with appropriate confidentiality and discretion.

MODULE V – RISK MANAGEMENT SYSTEMS

V.A. INTRODUCTION

It is recognized that at the time of authorization, information on the safety of a medicinal product is relatively limited. This is due to many factors including the relatively small numbers of subjects in clinical trials compared with the intended treatment population, restricted population in terms of age, gender and ethnicity, restricted co-morbidities, restricted co-medications, restricted conditions of use, relatively short duration of exposure and follow up, and the statistical problems associated with looking at multiple outcomes.

A medicinal product is authorized on the basis that in the specified indication(s), at the time of authorization, the benefit-risk balance is judged to be positive for the target population. A typical medicinal product will have multiple risks attached to it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorization is sought and many of the risks associated with the use of a medicinal product 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 characterise and quantify clinically relevant risks, and to identify new adverse reactions (the 'pharmacovigilance plan');
3. The planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

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

This module includes the principles of risk minimization, it should be read in conjunction with GVP Module XVI and GVP Module XVI Addendum I on educational materials.

V.A.1. Terminology

The definitions from GVP Annex I apply also for the purpose of this GVP Module. However, the RMP should focus on those risks that are relevant for the risk management activities for the authorized medicinal product.

From the **identified risks** of the medicinal product, the RMP should address only the risks that are undesirable clinical outcomes and for which there is sufficient scientific evidence that they are caused by the medicinal product. Reports of adverse reactions may be derived from multiple sources such as non-clinical findings confirmed by clinical data, clinical trials, epidemiological studies, and spontaneous data sources, including published literature. They may be linked to situations such as off label use, medication errors or drug interactions. Not all reported adverse reactions are necessarily considered a relevant risk of the product in a given therapeutic context.

From the **potential risks** of the medicinal product, the RMP should address only the risks that are undesirable clinical outcomes and for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal.

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 (see V.B.8.), 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 benefit-risk 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.

Missing information relevant to the risk management planning refers to 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.

V.B. STRUCTURE AND PROCESSES

V.B.1. 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 (see also V.A.1. and V.B.5.8.):

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

V.B.2. Responsibilities for risk management within an organization

The principle organizations directly involved in medicinal products' risk management planning are applicants/MAHs and the SFDA.

The MAH or applicant is responsible for:

- Having an appropriate risk management system in place;
- Ensuring that the knowledge and understanding on the product's safety profile, following its use in clinical practice, are critically reviewed. The MAH should monitor

pharmacovigilance data to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products and update the risk management system and the RMP accordingly, as described below. The critical review of the safety profile of the product is a continuous activity and is reflected in data submitted with PSUR/PBRER (see GVP Module VII), where an RMP submission may or may not be warranted. In addition, there are two specific milestones when the MAHs of products approved following full initial marketing authorization applications are advised to reflect on the need to review the list of safety concerns and the planned and ongoing pharmacovigilance and risk minimization activities:

- With the (first) 5-year renewal;
- In the time period when the first PSUR/PBRER following the first 5-year renewal is due for submission. It is anticipated that this PSUR/PBRER submission would occur approximately 8-9 years following the granting of the marketing authorization, at the time when the assessment of the initial marketing authorization applications for generic products for the active substance commences. As such, the safety profile of the medicinal product is likely to be sufficiently well characterized to allow for a critical review and update of the list of safety concerns.

V.B.3. Overview of the format and content of the risk management plan (RMP)

The RMP consists of seven parts. 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 (see V.C.1.1.). However, the RMP document is expected to be submitted as one single document including all modules and annexes, as relevant.

An overview of the parts and modules of the RMP is provided below in Table V.1.:

Table V.1. **Overview of the RMP parts and modules**

Part I	Product(s) overview
Part II	Safety specification
Module SI	Epidemiology of the indication(s) and target population(s)
Module SII	Non-clinical part of the safety specification
Module SIII	Clinical trial exposure
Module SIV	Populations not studied in clinical trials
Module SV	Post-authorization experience
Module SVI	Additional requirements for the safety specification
Module SVII	Identified and potential risks
Module SVIII	Summary of the safety concerns
Part III	Pharmacovigilance plan (including post-authorization safety studies)
Part IV	Plans for post-authorization efficacy studies
Part V	Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)
Part VI	Summary of the RMP
Part VII	Annexes

The amount of information, particularly in RMP part II, should be proportionate to the identified risk and the potential risk, and will depend on the type of medicinal product, its risks, and where it is situated in its life cycle.

The marketing authorization applicants/holders should adapt the RMPs of advanced medicinal products (ATMP), considering and discussing the anticipated post-authorization follow-up needs, focusing on particularities of these medicinal products. The specific RMP content requirements for ATMP should be discussed with the SFDA before the submission.

It is recommended, where appropriate, that the RMP document includes all relevant medicinal products from the same applicant/MAH containing the same active substance(s) (i.e. the RMP is an active substance-based document).

Information in the RMP should be provided in enough detail whilst avoiding unnecessary text that distracts from the key issues to be considered for risk management of the product. However, the safety specifications in the RMP should not be a duplication of data submitted elsewhere in the dossier, unless the sections are intended to be common modules with other documents such as the PSUR/PBRER. Where applicable, the information in the RMP should provide an integrated overview/discussion focusing on the most important risks that have been identified or are anticipated based on pre-clinical, clinical and post-marketing data presented in other modules of the eCTD. Any data included in the RMP should be consistent with other sections of the dossier. Links or references to relevant sections of the non-clinical and clinical overviews and summaries should be included in the RMP.

For new RMP submissions with limited safety data in the dossier, the RMP may contain the relevant safety data and discussion, to support the risk identification discussion.

To aid consistency between the information provided in the dossier and the RMP, Table V.2. indicates where information from the eCTD is likely to be discussed in the RMP. The eCTD data refers to the submission containing the RMP (e.g. initial marketing authorization applications and major variations) or to historical data already included in the dossier with previous submissions.

The RMP should be submitted as part of an eCTD submission; eCTD data/submissions in this Module should be read as eCTD or CTD data/submission, corresponding to the type of submission to the SFDA.

Table V.2. **Mapping between RMP modules and information in eCTD**

Part I Product(s) overview	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the indication(s) and target population(s)	Module 2.5 Clinical overview
Module SII Non-clinical part of the safety specification	Module 2.4 Non-clinical overview Module 2.6 Non-clinical written and tabulated summaries Module 4 Non-clinical study reports
Module SIII Clinical trial exposure	Module 2.7 Clinical summary Module 5 Clinical Study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post-authorization experience	Module 2.5 Clinical overview
Module SVI "Additional EU requirements for the safety specification"	Data not presented elsewhere in eCTD
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit-risk conclusion) Module 2.7 Clinical summary (SPC)
Module SVIII Summary of the safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance plan (including post- authorization safety studies)	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post-authorization efficacy studies	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part V Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)	Module 2.5 Clinical overview Module 2.7 Clinical summary

Only key literature referenced in the RMP should be included in RMP annex 7. This should be in the format of electronic links or references if already included elsewhere in eCTD (see V.B.10.).

The description of the parts and modules of an RMP in V.B.4. provides guidance on the main topics to be addressed within each specific area. However, some sections may not be relevant to all medicinal products and there may be additional topics that need to be included but are not mentioned in this guidance. 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 preliminary section of the RMP should include the following administrative information about the RMP document:

- Data lock point of the current RMP;
- Sign off date and the version number of the RMP;
- List of all parts and modules. For RMP updates, modules version number and date of approval (opinion date) should be tabulated in this section. High level comment on the rationale for creating the update should be included for significant changes to each module;

The evidence of oversight from the QPPV is not needed for versions submitted for assessment. The QPPV's actual signature or the evidence that the RMP was reviewed and approved by the QPPV should be included in the finalized approved version of the document; for eCTD submissions this would be the RMP with the last eCTD sequence of the procedure (e.g. closing sequence). The evidence of QPPV oversight can take the form of a statement that the RMP has been reviewed and approved by the MAH/applicant's QPPV and that the electronic signature is on file.

V.B.4. RMP part I "Product(s) overview"

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

Active substance information:

- Active substance(s);
- Pharmacotherapeutic group(s) (ATC code); name of the:

  - Marketing authorization applicant - for initial marketing authorization applications,

  or

  - MAH- for RMPs submitted with post-authorization procedures;
- Medicinal product(s) to which this RMP refers.
- Brief description of the product including:

- Chemical class;

- Summary of mode of action;

- Important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);

- eCTD link to the proposed product information, as appropriate;
- Indications: approved and proposed (if RMP submitted with an extension/restriction of indication);
- Dosage (summary information – only related to main population; not a duplication of SPC section 4.2);
- Pharmaceutical forms and strengths;
- Whether the product is subject to additional monitoring in the KSA (at initial marketing authorization application conclusion or with RMP updates).

V.B.5. RMP part II "Safety Specification"

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

plan.

The safety specification consists of eight RMP modules, of which RMP modules SI-SV, SVII and SVIII correspond to safety specification headings in ICH-E2E. RMP module SVI includes additional elements required to be submitted.

Although the elements outlined in V.B.5.2. to V.B.5.9. serve as a guide only, it is recommended that applicants/ MAHs follow the structure provided when compiling the safety specification.

Details of specific requirements for initial marketing authorization applications are included in V.C.1.1.

V.B.5.1. General Considerations for generic products and advanced therapy medicinal products

V.B.5.1.1. Generics

For generic medicinal products the expectation is that the safety specification is the same as that of the reference product or of other generic products for which an RMP is in place. If discrepancies exist between approved RMPs for such products, then the applicant is expected to propose and justify the most appropriate safety specification for their product. Exceptionally, the applicant for a new generic medicinal product may add or remove safety concerns compared with the safety profile of the reference product if this is appropriately justified (for example, when there is a more up to date understanding of the current safety profile or when there are differences in product characteristics compared with the reference product, e.g. there is a risk associated with an excipient present only in some of the products containing the same active substance).

V.B.5.1.2. Advanced therapy medicinal products

Certain products for human medicinal use are categorized in the KSA as advanced therapy medicinal products. These products broadly comprise:

- Gene therapy medicinal products;
- Somatic cell therapy medicinal products;
- Tissue engineered products.

Because of the nature of these products, risks may occur that are not normally a concern

with other medicinal products including risks to living donors, risks of germ line transformation and transmission of vectors. These risks need to be taken into consideration when developing the safety specification for ATMPs (see V.B.5.8.).

V.B.5.2. RMP part II, module SI "Epidemiology of the indication(s) and target population(s)"

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

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

V.B.5.3. RMP part II, module SII "Non-clinical part of the safety specification"

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

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

What constitutes an important non-clinical safety finding will depend upon the medicinal product, the target population and experience with other similar compounds or therapies in the same class. Normally, significant areas of toxicity (by target organ system) and the relevance of the findings to the use in humans should be discussed. Also, quality aspects

if relevant to safety (e.g. genotoxic impurities) should be discussed. If a product is intended for use in women of childbearing age, data on the reproductive/developmental toxicity should be explicitly mentioned and the implications for use in this population discussed. Where the non-clinical safety finding could constitute an important potential risk to the target population, it should be included as a safety concern in RMP module SVIII. Where the non-clinical safety finding is not considered relevant for human beings, provision of a brief explanation is required, but the safety finding is not expected to be carried forward to SVII and SVIII as a safety concern.

If, based on the assessment of the non-clinical or clinical data, additional non-clinical studies are considered warranted and proposed to be part of the pharmacovigilance plan, this should be briefly discussed here.

Final conclusions on this section should be aligned with content of module SVII and any safety concerns should be carried forward to module SVIII.

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

V.B.5.4. RMP part II, module SIII "Clinical trial exposure"

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

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

- Age and gender;
- Indication;
- Dose;
- Other stratifications should be provided where this adds meaningful information for risk management planning purposes (e.g. ethnic origin).

Pediatric data should be divided by age categories (e.g. ICH-E11); similarly, the data on older people should be stratified into age categories reflecting the target population (e.g. 65-74, 75-84 and 85 years and above).

Unless clearly relevant and duly justified, data should not be presented by individual trial, but pooled. Totals should be provided for each table/graph as appropriate. Where patients have been enrolled in more than one trial (e.g. open label extension study following a trial) they should only be included once in the age/gender/ethnic origin tables. Reasons for differences in the total numbers of patients between tables should be explained.

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

V.B.5.5. RMP part II, module SIV "Populations not studied in clinical trials"

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

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

If the product is expected to be used in populations not studied and if there is a scientific rationale to suspect a different safety profile, but the available information is insufficient to determine whether or not the use in these circumstances could constitute a safety concern, then this should be included as missing information in the RMP. Excluded populations from

the clinical trial development program should be included as missing information only when they are relevant for the approved and proposed indications, i.e. “on-label”, and if the use in such populations might be associated with risks of clinical significance. In discussing differences between target populations and those exposed in clinical trials it should be noted that some differences may arise through trial setting (e.g. hospital or general practice) rather than through explicit inclusion/exclusion criteria. When such populations are proposed as missing information, then RMP module SIV should also include a discussion on the relevant subpopulations.

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

V.B.5.6. RMP part II, module SV “Post-authorization experience”

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

It should only provide an overview of experience in the post-authorization phase that is helpful for risk management planning purposes. It is not the intention to duplicate information from the PSUR/PBRER.

Additionally, a discussion on how the medicinal product is being used in practice and on-label and off- label use, including use in the special populations mentioned in RMP module SIV, can also be included when relevant for the risk identification discussion in module SVII.

Where appropriate and relevant for the discussion in SVII, data on use in markets outside the KSA from indications not authorized in KSA should also be summarized, and the implications for the authorization in the KSA should be discussed.

V.B.5.7. RMP part II, module SVI “Additional requirements for the safety specification”

In addition to safety topics required by ICH-E2E, the following should be addressed in the RMP: the potential for misuse for illegal purposes, and, where appropriate, the proposed risk minimization measures, e.g. limited pack size, controlled access program, special medical prescription (see also V.B.8.).

V.B.5.8. RMP part II, module SVII "Identified and potential risks"

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

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

- Potential harm from overdose, whether intentional or accidental, for example in cases where there is a narrow therapeutic margin or potential for major dose-related toxicity, and/or where there is a high risk of intentional overdose in the treated population (e.g. in depression). Where harm from overdose has occurred during clinical trials this should be explicitly mentioned and, where relevant, the important risks following overdose should be included as safety concerns in RMP module SVIII and appropriate risk minimization proposed in RMP part V;
- Potential for risks resulting from medication errors, defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. Medication errors leading to important risks, identified during product development including clinical trials, should be discussed and information on the errors, their potential cause(s) and possible remedies given. Where applicable an indication should be given of how these have been considered in the final product design. Important risks related to medication errors in the post marketing period should be discussed in the updated RMP and ways of limiting the errors proposed;
- Potential for transmission of infectious agents due to the nature of the manufacturing process or the materials involved. For live attenuated vaccines any potential for transmission of mutated live vaccine virus, and the potential of causing the disease in immunocompromised contacts of the vaccine should be discussed with the view of considering them as important potential risks;
- Potential for off-label use, when differences in safety concerns between the target and the off-label population are anticipated, the potential risks arising from the off-label use of the product should be considered for inclusion in the safety specifications;

- If an important identified or potential risk common to other members of the pharmacological class is not thought to be an important identified or important potential risk with the concerned medicinal product, the evidence to support this should be provided and discussed;
- Important risks related to identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to the treatments for the condition, but also in relation to commonly used medications in the target population. The evidence supporting the interaction and possible mechanism should be summarized, the potential health risks discussed for different indications and populations and plans to further characterize and minimize the risks described. Important risks derived from interactions should be included as a safety concern;
- Risks in pregnant and lactating women, e.g. teratogenic risk - direct or through exposure to semen: contraception recommendations can be considered as risk minimization measures. Further guidance on risk management in case of exposure of the embryo / fetus to teratogenic agents can be found in the GVP P.III. and GVP Module XVI;
- Effect on fertility - appropriate risk minimization measures should be considered, e.g. routine risk communication and/or additional activities recommending fertility preservation: sperm cryopreservation in men and embryo and oocyte cryopreservation in women;
- Risks associated with the disposal of the used product (e.g. transdermal patches with remaining active substance or remains of radioactive diagnostics);
- Risks related to the administration procedure (e.g. risks related to the use of a medical device (malfunction which impacts on the dose administered, risk of variability in complex administrations);
- Pediatric safety issues that are particular causes of concern in pediatric population, as described in section 5 of annex I of the PIP opinion (Potential long-term safety/efficacy issues in relation to pediatric use for consideration in the RMP/Pharmacovigilance activities).

For RMPs of ATMPs, the applicants should also consider the possible specific risks in drafting the safety specifications.

V.B.5.8.1. RMP part II, module SVII section "Identification of safety concerns in the initial RMP submission"

This RMP section should contain the initial identification of safety concerns and is expected to be populated with the initial submission of an RMP, either at the time of the initial marketing authorization (MA) application or post-authorization (i.e. for approved products that previously did not have an RMP).

This section is expected to be "locked" and not change after the approval of the initial RMP.

V.B.5.8.1.a. RMP part II, module SVII sections "Risk considered important for inclusion in the list of safety concerns" and "Risk not considered important for inclusion in the list of safety concerns"

In this RMP section the following information should be summarized and discussed:

- Risk seriousness;
- Risk frequency;
- The benefit-risk impact of the risks.

For risks not taken forward as safety concerns, the information can be grouped by reasons for not including them as safety concerns.

V.B.5.8.2. RMP part II, module SVII section "New safety concerns and reclassification with a submission of an updated RMP"

In the post-authorization phase, it is expected that new identified and potential risks of the product are presented in the safety section of the dossier (with e.g. signal evaluation, periodic benefit-risk evaluation, or safety variations procedures) together with an evaluation on whether the risks should be considered important and added in the safety specification in the RMP. This discussion should not be duplicated in the RMP, but the details of any new important identified or potential risk should be included in the RMP section described in V.B.5.8.3.

When an important identified or potential risk or missing information is re-classified or removed, a justification should be provided in this RMP section, with appropriate reference to the safety data. The information included in this section may take the form of a statement describing a previous regulatory request, with a reference to the procedure where such request was formulated.

V.B.5.8.3. RMP part II, module SVII section "Details of important identified risks, important potential risks, and missing information"

For RMPs containing multiple products, if there are significant differences between products (e.g. fixed dose combination products) it is appropriate to make it clear which safety concerns relate to which product.

This RMP section applies to all stages of the product's life cycle.

Presentation of important identified risks and important potential risks data:

- Name of the risk (using MedDRA terms when appropriate);
- potential mechanism;
- Evidence source(s) and strength of the evidence (i.e. the scientific basis for suspecting the association);
- Characterization of the risk: e.g. frequency, absolute risk, relative risk, severity, reversibility, long- term outcomes, impact on quality of life;
- Risk factors and risk groups (including patient factors, dose, at risk period, additive or synergistic factors);
- Preventability (i.e. predictability of a risk; whether risk factors have been identified that can be minimized by routine or additional risk minimization activities other than general awareness using the PI; possibility of detection at an early stage which could mitigate seriousness);
- Impact on the benefit-risk balance of the product;
- Public health impact (e.g. absolute risk in relation to the size of the target population and consequently actual number of individuals affected, or overall outcome at population level).

Presentation of missing information data:

- Name of the missing information (using MedDRA terms when appropriate);
- Evidence that the safety profile is expected to be different than in the general target population;
- Description of a population in need of further characterization, or description of the risk anticipated in the population not studied, as appropriate.

V.B.5.9. RMP part II, module SVIII "Summary of the safety concerns"

In this RMP module, a list of safety concerns should be provided with the following

categories:

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

V.B.6. RMP part III "Pharmacovigilance plan (including post-authorization safety studies)"

The purpose of the pharmacovigilance plan in part III of the RMP is to present an overview and discuss how the applicant/MAH 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 the SFDA and the applicant/MAH 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.

V.B.6.1. RMP part III section "Routine pharmacovigilance activities"

Routine pharmacovigilance is the primary/minimum set of activities required for all medicinal products as per the obligations set out in this guidance. Signal detection, which is part of routine pharmacovigilance, is an important element in identifying new risks for all products. The descriptions of these activities in the pharmacovigilance system master file (see GVP Module II) are not required to be repeated in the RMP.

The SFDA may make recommendations for specific activities related to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions which differ from the normal requirements for routine pharmacovigilance (see GVP Module I). If these recommendations include recording of tests (including in a structured format) that would form part of standard clinical practice for a patient experiencing the adverse reaction, then this requirement would still be considered routine. The routine pharmacovigilance section of the pharmacovigilance plan should be used in these circumstances to explain how the applicant will modify its routine pharmacovigilance activities to fulfil any special committee and the SFDA recommendations on routine pharmacovigilance.

However, if the recommendation includes the submission of tissue or blood samples to a specific laboratory (e.g. for antibody testing) that is outside standard clinical practice, then this would constitute an additional pharmacovigilance activity.

This RMP section should describe only the routine pharmacovigilance activities beyond adverse reaction reporting and signal detection.

V.B.6.1.1. Specific adverse reaction follow-up questionnaires

Where an applicant/MAH is requested, or plans, to use specific questionnaires to obtain structured information on reported suspected adverse reactions of special interest, the use of these materials should be described in the routine pharmacovigilance activities section and copies of these forms should be provided in RMP annex 4.

Without prejudice to the originality of the format of the questionnaire(s), it is in the interest of public health that questionnaire(s) used by different applicants/MAHs for the same adverse event should be kept as similar as possible, in order to deliver a consistent message and to provide useful data for the analysis of the reports, which are relevant for regulatory decisions, while decreasing the burden on healthcare professionals.

Therefore, MAHs are strongly encouraged to share the content of their questionnaire(s) upon request from other MAHs.

V.B.6.1.2. Other forms of routine pharmacovigilance activities

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

V.B.6.2. RMP part III section "Additional pharmacovigilance activities"

The applicant/MAH 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 benefit-risk 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 the SFDA 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.

Studies in the pharmacovigilance plan should be designed and conducted according to the respective legislation in place, and recommendations in the GVP Module VIII.

Study protocols may be included for evaluation in an RMP update only when the studies are included in the pharmacovigilance plan and the protocols submission has been requested by the SFDA. Reviewed and approved protocols for studies in the pharmacovigilance plan should be provided in RMP annex 3 – part C (or electronic links or references to the protocol included in other section of the eCTD dossier). Other category 3 studies protocols, submitted for information only, may also be included in RMP annex 3 – part C. Protocols of completed studies should be removed from RMP annex 3 once the final study reports are submitted to the SFDA for assessment and the study is removed from the pharmacovigilance plan (see V.B.10.3.).

The milestones for the final study report submission to the SFDA should be included for all studies in the pharmacovigilance plan.

MAHs may also submit to the SFDA protocols of post-authorization safety studies (PASS) for scientific advice.

V.B.6.3. RMP part III section "Summary table of additional pharmacovigilance activities"

This RMP section outlines the pharmacovigilance activities designed to identify and characterize risks associated with the use of a medicinal product. Some may be imposed as conditions to the marketing authorization, either because they are key to the benefit-risk profile of the product (category 1 studies in the pharmacovigilance plan), or because they are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (category 2 studies in the pharmacovigilance plan).

Other studies might be required in the RMP to investigate a safety concern or to evaluate the effectiveness of risk minimization activities. Such studies included in the pharmacovigilance plan are also legally enforceable (category 3 studies in the pharmacovigilance plan).

For generic products, the pharmacovigilance plan will reflect the outstanding needs for pharmacovigilance investigations at the time of their approval. In some cases, ongoing or planned PASS for the originator product would also be required to be conducted for the generic products (e.g. registries may need to be in place to include most/all patients treated with the medicine, be it generic or originator products). Where applicable, the MAHs are encouraged to set up joint PASS, for instance in the case of registries or when a referral has resulted in an imposed PASS for all authorized medicinal products containing a named substance in a specified indication.

V.B.7. RMP part IV "Plans for post-authorization efficacy studies"

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

V.B.8. RMP part V "Risk minimization measures (including evaluation of the effectiveness of risk minimization activities)"

Part V of the RMP should provide details of the risk minimization measures which will be

taken to reduce the risks associated with respective safety concerns.

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimization plan specific to each product. i.e. products where the indications lie in different medical specialties and have different safety concerns associated; products where risks differ according to the target population; products with different legal status for the supply of medicinal products to patients.

The need for continuing risk minimization measures should be reviewed at regular intervals and the effectiveness of risk minimization activities assessed (see V.B.8.). Guidance on additional risk minimization measures and the assessment of the effectiveness of risk minimization measures is provided in GVP Module XVI and GVP Module XVI Addendum I – Educational materials.

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 (e.g. on inner and outer carton);
- The package leaflet;
- The pack size(s);
- The legal status of the product.

Even the formulation itself may play an important role in minimizing the risk of the product.

Summary of product characteristics (SPC) 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. The Guideline on Summary of Product Characteristics provides guidance on how information should be presented.

Both materials provide routine risk minimization recommendations; however, there are two types of messages the SPC and PL can provide:

1. **Routine risk communication messages**: usually found in section 4.8 of the SPC or section 4 of the PL; these messages communicate to healthcare professionals and patients

the undesirable effects of the medicinal product, so that an informed decision on the treatment can be made;

2. **Routine risk minimization activities recommending specific clinical measures to address the risk:** usually found in sections 4.2 and 4.4 of the SPC but can also be found in sections 4.1, 4.3, 4.5, 4.6, 4.7 and 4.9, and sections 2 and 3 of the PL; warning and precaution messages and recommendations in the SPC will include information on addressing the risk of the product by e.g.:

- Performing a test before the start of treatment;
- Monitoring of laboratory parameters during treatment;
- Monitoring for specific signs and symptoms;
- Adjusting the dose or stopping the treatment when adverse events are observed, or laboratory parameters change;
- Performing a wash-out procedure after treatment interruption;
- Providing contraception recommendations;
- Prohibiting the use of other medicines while taking the product;
- Treating or preventing the risk factors that may lead to an adverse event of the product;
- Recommending long-term clinical follow-up to identify in early stages delayed adverse events.

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.

The marketing authorization 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. This 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 medical prescription. It may also restrict where the medicinal product can be administered (e.g. in a hospital) or by whom it may be prescribed (e.g. specialist).

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

Restricted medical prescription

This may be used to control who may initiate treatment, prescribe the medicinal product and the setting in which the medicinal product can be given or used. When considering classification of a medicinal product as subject to restricted medical prescription, the following factors shall be considered:

- The medicinal product, because of its pharmaceutical characteristics or novelty or in the interests of public health, is reserved for treatments which can only be followed in a hospital environment.
- The medicinal product is used in the treatment of conditions which must be diagnosed in a hospital environment or in institutions with adequate diagnostic facilities, although administration and follow-up may be carried out elsewhere.
- The medicinal product is intended for outpatients, but its use may produce very serious adverse reactions requiring a prescription drawn up as required by a specialist and special supervision throughout the treatment.

Special medical prescription

For classification as 'subject to special medical prescription', the following factors shall be considered:

- The medicinal product contains, in a non-exempt quantity, a substance classified as a narcotic or a psychotropic substance within the meaning of the international conventions in force, such as the United Nations Conventions of 1961 and 1971;

- The medicinal product is likely, if incorrectly used, to present a substantial risk of medicinal abuse, to lead to addiction or be misused for illegal purposes, or
- The medicinal product contains a substance which, by reason of its novelty or properties, could be considered as belonging to the group envisaged in the second indent as a precautionary measure.

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.

Where relevant, key messages of additional risk minimization activities should be provided in RMP annex 6 – Details of proposed additional risk minimization activities.

Further guidance on additional risk minimization measures is provided in GVP Module XVI.

Evaluation of the effectiveness of risk minimization activities

When the RMP is updated, the risk minimization plan should include a discussion of the impact of additional risk minimization activities.

A discussion on the results of any formal assessment(s) of risk minimization activities should be included when available. If a particular risk minimization strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then consideration should be given to alternative activities. The MAH should comment in the RMP on whether additional or different risk minimization activities are needed for each safety concern or whether in their view the (additional) risk minimization measures may be removed (e.g. when risk minimization measures have become part of standard clinical practice).

If a study to evaluate the effectiveness of risk minimization activities is required or imposed by the SFDA, the study should be included in the pharmacovigilance plan, part III of the RMP.

Guidance on monitoring the effectiveness of risk minimization activities is included in the GVP Module XVI.

V.B.8.1. RMP part V section "Risk minimization plan"

In the RMP section on the risk minimization plan, for each safety concern in the safety specification, the following information should be provided:

- Routine risk minimization activities, including details of whether only inclusion in the SPC and PL is foreseen, or any other routine risk minimization activities are proposed;
- Additional risk minimization activities (if any), including individual objectives and justification of why needed, and how their effectiveness will be measured.

V.B.8.2. RMP part V section "Summary of risk minimization measures"

A table listing the routine and additional risk minimization activities by safety concern should be provided in this RMP section (e.g. the SPC section number where the risk appears in the SPC, the list of educational materials).

V.B.9. RMP part VI "Summary of the risk management plan"

A summary of the RMP for each authorized medicinal product shall be made publicly available and shall include the key elements of the RMP.

Part VI of the RMP shall be provided by the marketing authorization applicant/holder for medicinal products which have an RMP. The RMP summary should be updated when important changes are introduced into the full RMP. Changes should be considered important if they relate to the following:

- New important identified or potential risks or important changes to or removal of a safety concern;
- Inclusion or removal of additional risk minimization measures or routine risk minimization activities recommending specific clinical measures to address the risk;
- Major changes to the pharmacovigilance plan (e.g. addition of new studies or completion of ongoing studies).

The audience of RMP summaries is very broad. To ensure that the summary can satisfy the different needs, it should be written and presented clearly. However, this does not mean that technical terms should be avoided. The document should clearly explain its purpose and how it relates to other information, in particular the product information (i.e. the SPC, the PIL and

the labelling).

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

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

V.B.10. RMP part VII "Annexes to the risk management plan"

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

V.B.10.1. RMP annex 1

Annex 1 of the RMP is the structured electronic representation of the RMP. It is not required to be submitted in eCTD. This annex can be left empty in the RMP document.

V.B.10.2. RMP annex 2: Tabulated summary of planned, on-going, and completed pharmacovigilance study program

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

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

V.B.10.3. RMP annex 3: Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 3 should not include protocols of studies not imposed nor requested by the SFDA (i.e. not in the pharmacovigilance plan). This annex may include the electronic links or references to other modules of the eCTD dossier where the protocols are included, instead of the full protocol documents.

V.B.10.3.1. RMP annex 3 – part A: Requested protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP

If protocols have been requested to be submitted for review by the SFDA, and the MAH choses to submit for assessment a study protocol within the same procedure as the RMP submission, part A should include this protocol; alternatively, the protocol might be reviewed in a stand-alone procedure, and once agreed, included in the RMP annex 3 – part C. The regulatory pathway for the protocol submission should be agreed with the SFDA.

V.B.10.3.2. RMP annex 3 – part B: Requested amendments of previously approved protocols of studies in the pharmacovigilance plan, submitted for regulatory review with this updated version of the RMP

If protocols amendments have been requested to be submitted for review by the SFDA, and the MAH choses to submit for assessment the study protocol amendment within the same procedure as the RMP submission, part B should include the updated protocol; alternatively, the protocol amendment might be reviewed in a stand-alone procedure, and once agreed, included in the RMP annex 2 – part C. The regulatory pathway for the protocol submission should be agreed with the SFDA.

Once approved, protocols from parts A or B should be moved to part C, with the next warranted RMP update.

V.B.10.3.3. RMP annex 3 – part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the SFDA

Previously agreed protocols for on-going studies and final protocols not reviewed by the SFDA should be included in this part C of RMP annex 3, as follows:

- The full protocols that have been previously assessed by the SFDA and agreed (i.e. no protocol resubmission was requested). The protocols should be accompanied by the name of the procedure when the protocol was approved and date of the outcome. This may include the electronic link or reference to other modules of the eCTD dossier where the protocols have been previously submitted, instead of the full protocol documents.
- The final protocols of other category 3 studies: protocols that were not requested to be reviewed by the SFDA and are submitted by the MAH for information only.

Protocols of completed studies should be removed from this annex once the final study reports are submitted to the SFDA for assessment.

V.B.10.4. RMP annex 4: Specific adverse event follow-up forms

This annex should include all follow-up forms used by the MAH to collect additional data on specific safety concerns. The usage of follow-up forms included in this annex should be detailed in the pharmacovigilance plan in the RMP, as routine pharmacovigilance activities. The forms that should be included in this annex are sometimes known as “event follow-up questionnaire”, “adverse event data capture/collection aid” or “adverse reaction follow-up form”.

V.B.10.5. RMP annex 5: Protocols for proposed and on-going studies in RMP part IV

This annex should include links or reference to other parts of the eCTD dossier, where the protocols for an imposed efficacy study are already included, for studies included in RMP part IV.

V.B.10.6. RMP annex 6: Details of proposed additional risk minimization activities

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

V.B.10.7. RMP annex 7: Other supporting data (including referenced material)

When applicable, to avoid duplication of the materials presented as references, this annex should include eCTD links or reference to other documents included in other modules of the dossier.

V.B.10.8. RMP annex 8: "Summary of changes to the risk management plan over time"

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

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

V.B.10.9. RMP annex 9: Saudi-Specific Annex (SSA):

The MAH must submit the SSA whenever an EU RMP (or alternative RMP where no current EU RMP exists) is submitted in pre-marketing during registration and post marketing phase where the RMP is updated or required for submission.

The only situation where a SSA is not routinely required is if the RMP has been prepared specifically for Saudi Arabia.

The Saudi-specific annex (SSA) provides details not included in the EU RMP that enables the EU RMP (or, core or global RMP if no current EU RMP exists) to be adapted to the Saudi context. The SSA is required:

- To document any differences in safety concerns between the EU and Saudi (which may include differences in the frequency, severity or nature of safety concerns resulting from differences in the epidemiology of the indication and target population) and ensure that these are taken into account in determining an adequate risk management system
- To document any risk management activities not reflected in the EU RMP that are required to adequately address the safety concerns in Saudi Arabia (such as additional risk minimisation measures required by the SFDA)
- To record details of the dissemination and evaluation of effectiveness of risk minimisation activities in Saudi.
- To record milestones and timelines for reporting on additional pharmacovigilance and risk minimisation activities to the SFDA

V.B.10.9.1 Format and content of the SSA:

1. **Product details**

Active ingredient(s):	
Product name (s):	
Marketing Authorization Holder (MAH):	
SSA version:	
Related EU-RMP version*:	

*Can be changed to 'core' or 'global' RMP if no EU-RMP is available.

2. **Safety specification**

2.1. Epidemiology of the indication(s) and target population(s) in Saudi Arabia

Include information such as epidemiology of the medical condition(s) or risk factors that reflect the authorized indication(s) in Saudi Arabia, where available.

Include special considerations to genetic or extrinsic factors that are specific to the Saudi population.

Include information on the use of product in Saudi Arabia, Saudi patient exposure and post-authorization experience in Saudi Arabia.

2.2. Saudi-specific safety concerns

To list the important safety concerns relevant in the Saudi context.

Include details of any safety concerns for Saudi Arabia that are additional to those proposed in the EU-RMP, or to include any differences in the frequency, severity or nature of safety concerns in EU RMP, resulting from differences in the epidemiology of the indication and target population in Saudi Arabia.

3. **Pharmacovigilance Plan**

3.1 Routine Pharmacovigilance activities in Saudi Arabia

Provide a list of routine pharmacovigilance activities that will be/ implemented in Saudi Arabia, to address the safety concerns.

3.2 Additional Pharmacovigilance activities in Saudi Arabia

This section should indicate whether there are additional pharmacovigilance activities for Saudi-specific safety concern, or for safety concerns listed in the EU-RMP and provide the details of any additional pharmacovigilance activities that will be/implemented in Saudi.

Table 1: Summary table of additional pharmacovigilance activities in Saudi Arabia:

Study and status	Objectives	Safety concerns addressed	Study location; Saudi patients included in the study?	Planned date for submission of (interim and) final results
E.g. Study1 Planned			Multinational; yes	
E.g. Registry2 Planned			Saudi Arabia; yes	

4. Risk minimization measures

4.1 Saudi-specific routine risk minimization measures (required for all products)

This section should describe the routine risk minimization used for each safety concern. You should provide a reference to the Saudi PIL and SPC sections, identify and justify any differences between the statements in the EU SPC and PIL, and Saudi SPC and PIL, with justification.

Table 2: Saudi-specific routine risk minimization measures:

Safety concern	Routine risk minimization activities	Differences between EU and Saudi routine risk minimization activities, with justification
Important identified risks		
Risk 1	Saudi PIL section	
	Saudi SPC section	
	Other measures: [e.g. pack size, package leaflet, warning on pack]	
Important potential risks		
Risk 1	Saudi PIL section	
	Saudi SPC section	
	Other measures: [e.g. pack size, package leaflet, warning statement on pack]	
Important missing information		
Risk 1	Saudi PIL section	
	Saudi SPC section	
	Other measures: [E.g., pack size, package leaflet, warning statement on pack].	

4.2 Additional risk minimization measures in Saudi Arabia

This section should:

- Indicate all the additional risk minimization measures that will be/ implemented in Saudi Arabia, and any risk minimization activities not reflected in the EU RMP that are required to adequately address the safety concerns in Saudi Arabia.
- Indicate whether there are additional risk minimization activities for Saudi-specific safety concern, or Saudi-specific additional risk minimization measures for safety concerns listed in EU RMP and provide the detail of any additional risk minimization measures.

If there are no additional safety concerns for Saudi Arabia, and/or no Saudi-specific risk minimization activities for safety concerns listed in the EU-RMP then this can be simply stated.

If you propose to remove an additional risk minimization activity in Saudi Arabia, you should provide a justification. The justification may refer to information provided in the EU RMP. If the justification relies on evidence presented in the EU RMP (such as from the evaluation of effectiveness of risk minimization activities), you should provide a rationale for the applicability of the evidence in Saudi Arabia and preferably using supporting evidence from Saudi Arabia.

Table 3: Additional risk minimization measures in Saudi Arabia

Type of additional risk minimization activity	Objectives	Rationale for the additional risk minimization activity:	Saudi-specific additional risk minimization measures?
E.g. Prescriber guide	Include objectives and a list of risks addressed.	Include justification on why the particular additional risk minimization is considered needed.	Yes, justification
E.g. Patient guide			no

Provide copies of draft of additional risk minimization measures that /will be implemented in Saudi Arabia in the Appendix in this Saudi-specific Annex (SSA). For digital additional risk minimisation tools, provide content and images of the on-screen layout of the information, and/or the login details or access codes to enable the SFDA to evaluate the safety content in the format in which it is provided to the end user.

4.3 How additional risk minimization measures will be implemented in Saudi Arabia.

Provide a table describing the implementation of all planned additional risk minimisation measures for Saudi Arabia, including:

- The target audience for each activity.
- How it will be implemented (including how materials will be disseminated).
- anticipated timeframes for implementation (such as expected start date for activity/dissemination and frequency of repetition, if relevant).

Table 4: Implementation of additional risk minimization measures in Saudi Arabia (example)

Additional risk minimization measures	Target audience	Distribution scope	Risks addressed	Implementation details, including method(s) of dissemination	Distribution start date and frequency of repetition, if relevant)
e.g. Healthcare provider guide	Physician Pharmacist	Specialties of targeted healthcare providers. e.g. cardiologists		E.g., paper copies delivered to physicians and pharmacists.	At launch Repeat at 18 months after launch
e.g. patient guide	Patients			E.g., paper copies delivered to physicians to provide to patients.	At launch Repeat at 18 months after launch

4.4. How additional risk minimization measures will be evaluated in Saudi Arabia

Describe the evaluation of each additional risk minimization activity to be conducted in Saudi Arabia, including:

- How and when each activity will be evaluated
- How and when evaluation results will be reported to the SFDA

You must demonstrate that your risk minimization program has been implemented as planned and is effective, and if not, what actions will be taken to improve effectiveness. Your plan(s) to measure effectiveness should include a clear description of what defines success prior to implementation.

In the evaluation plan, you should consider the use of process or outcome indicators.

Table 5: indicators for evaluating the effectiveness of risk minimization measures:*

Process indicators	Outcome indicators
Reaching the target population	The safety outcome of the risk minimization program, such as the frequency and/or severity of adverse reactions.
Assessing clinical knowledge	
Assessing clinical actions	

*For further guidance regarding the evaluation of risk minimization measures, refer to Module XVI– Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators

Table 6: Planning the evaluation of the effectiveness of risk minimization activities:*

Additional risk minimization activity	Evaluation plan and criteria for success	Timeframe for conduction and results submission
e.g. Health professional guide and checklist	The methods proposed for evaluating the effectiveness of risk minimization measures should be described (e.g. surveys, drug utilization study,...). The aspects that will be assessed should be described i.e. reaching the target population, clinical knowledge, or clinical actions. The definition for a successful implementation should be predefined.	The timeframe should describe when the effectiveness of risk minimization measures would take place. It should be described when and how the results of the evaluation will be delivered to SFDA.

* The table above should be filled for each risk minimization measure prior to its approval. Whether the evaluation would assess process or outcome indicators. For further information regarding the evaluation of risk minimization measures, refer to Module XVI– Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators

5. Appendix

<Protocols of additional pharmacovigilance activities>

<Draft of additional risk minimization measures that /will be implemented in Saudi Arabia>

<Protocols for the evaluation of the effectiveness of risk minimization activities in Saudi Arabia>

<Other related documents, if any>

V.B.11. The relationship between the risk management plan and the periodic safety update report

The primary post-authorization pharmacovigilance documents for safety surveillance are the RMP and the PSUR/PBRER. Although there is some overlap between the documents, the main objectives of the two are different and the situations when they are required are not always the same. Regarding objectives, the main purpose of the PSUR/PBRER is retrospective, integrated, post-authorization benefit-risk assessment whilst that of the RMP is prospective pre-and post-authorization benefit-risk management and planning. As such, the two documents are complementary.

When a PSUR/PBRER and an RMP are submitted together, the RMP should reflect the conclusions of the accompanying PSUR/PBRER. For example, if a new signal is discussed in the PSUR/PBRER and the PSUR/PBRER concludes that this is an important identified or important potential risk to be added in the RMP, the important risk can be added in the updated RMP submitted with the PSUR/PBRER. The pharmacovigilance plan and the risk minimization plan should be updated to reflect the MAH's proposals to further investigate the safety concern and minimize the risk.

Table V.3. Periodic safety update report and risk management plan modules containing similar information (however, may not be in identical format and may not be interchangeable)

RMP section	PSUR section
Part II, module SIII – "Clinical trial exposure"	Sub-section 5.1 "Cumulative subject exposure in clinical trials"
Part II, module SV – "Post-authorization experience"	Sub-section 5.2 "Cumulative and interval patient exposure from marketing experience"
Part II, module SVII – "Identified and potential risks" and part II, module SVIII – "Summary of the safety concerns"	Sub-sections 16.1 "Summaries of safety concerns" and 16.4 "Characterization of risks"
Part V – "Risk minimization measures", section "Evaluation of the effectiveness of risk minimization activities"	Sub-section 16.5 – "Effectiveness of risk minimization (if applicable)"

V.B.12. 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 MAH is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in GVP Module I. The MAH should maintain records of when RMPs were submitted to the SFDA 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.

V.C. OPERATION WITHIN THE KSA

V.C.1. Requirements for the applicant/MAH in the KSA

For all new marketing applications, the applicant shall submit the RMP describing the risk management system, together with a summary. SSA must be submitted with the RMP in pre-marketing during registration and post marketing phase where the RMP is updated or required for submission (see V.B.10.9.). The SSA is not required only if the RMP was prepared specifically for Saudi Arabia.In the post-authorization phase, an RMP update or a new RMP may need to be submitted at any time:

- At the request of the SFDA when there is a concern about a risk affecting the benefit-risk balance.
- With an application involving a change to an existing marketing authorization when the data included leads to a change in the list of safety concerns, The RMP update may be warranted as a result of data submitted with applications such as a new or significant change to the indication, a new dosage form, a new route of administration, a new manufacturing process of a biotechnologically-derived product.
- or when a new additional pharmacovigilance activity or a risk minimization activity is needed or is proposed to be removed. and after the approval of the new additional risk minimization activity.

The need for an RMP or an update to the RMP should be discussed with the SFDA, as appropriate, well in advance of the submission of an application involving a significant change to an existing marketing authorization. Post-authorization RMPs can be submitted through e-mail (DS@sfda.gov.sa).

V.C.1.1. Risk management plans with initial marketing authorization applications

For full initial marketing authorization applications, all parts of an RMP should be submitted (see V.B.4.). For other types of initial marketing authorization applications, the requirements for the RMP content follow the concept of proportionality to the identified risks and potential risks of the medicinal product, and the need for post-authorization safety data; therefore, certain parts or modules may have reduced content requirements or may be left empty, where not applicable.

Table V.4. Summary of minimum RMP requirements for initial marketing authorization applications (for full description see text below)

Product	Part I	Part II								Part III	Part IV	Part V	Part VI
		SI	SII	SIII	SIV	SV	SVI	SVII	SVIII				
0. Full MA application	√	√	√	√	√	√	√	√	√	√	√	√	√
1. Generic product	√							‡	√	√	*	∫	√
2. Informed consent product	√	√	√	√	√	√	√	√	√	√	√	√	√
3. Hybrid product	√	†		†				†	√	√	√	∫	√
4.a. Fixed combination product – new active substance	√	∓	∓	∓	∓	∓	∓	√	√	√	√	√	√
4.b. Fixed combination product – no new active substance	√		†	†				‡	√	√	*	∫	√
5. Well stablished medicinal use product	√							√	√	√	√	√	√
6. Biosimilar product	√		√	√	√	√	√	√	√	√	√	√	√

√ = applicable/relevant
‡ = relevant only if "originator" product does not have an RMP and its safety profile is not published on CMDh website
* = relevant only when a PAES was imposed for the "originator" product
∫ = statement of alignment of safety information in PI is sufficient
† = requirements based on risk proportionality principle, addressing new data generated

or differences
with the “originator” product
T̄ = focus on the new active substance

V.C.1.1.1. New applications, i.e. “generic”

The elements for new applications are as following:

- RMP part I: The elements are the same as for initial marketing authorization application for a full application.
- RMP part II: there are two situations possible:

1. The originator product has an RMP: RMP modules SI-SVII may not be applicable. Module SVIII should include the summary of the safety concerns, in line with the originator product. If the applicant considers that the available evidence justifies the removal or the change of a safety concern, then data in module SVII should also be included to address the safety concern and detailing the applicant’s arguments. Similarly, if the applicant has identified a new safety concern specific to the generic product (e.g. risks associated with a new excipient or a new safety concern raised from any clinical data generated), this should be discussed and the new safety concern detailed in module SVII.

2. The originator product does not have an RMP: Full modules SVII and SVIII should be included in the RMP. Module SVII should critically analyze available relevant information (e.g. own pre-clinical and clinical data, scientific literature, originator product’s product information) and propose a list of important identified and potential risks as well as missing information.

- RMP part III: This should include a description of the routine pharmacovigilance activities, as detailed in V.B.6.1.. The applicant is strongly encouraged to contribute to and participate in the planned or ongoing studies performed by the marketing authorization holder of the originator product, when it is important that all available (prospective) data is collected in one study. This may be the case for instance when data from patients using the new product are important to further characterize the safety profile of the substance and enrolling patients in separate studies with the same or similar objectives creates an unnecessary burden on patients, clinicians or investigators (e.g. pregnancy registries, disease registries, any PASS evaluating long-term use). The SFDA may also consider imposing studies to be conducted for generic

products as applicable (e.g. within the context of referrals when generic products are involved or as consequence of the outcome of a referral imposing a study to the originator product).

- RMP part IV: This part of the RMP may be left empty unless a PAES has been imposed to be conducted for the generic product (e.g. following a referral).
- RMP part V: When the originator product does not have additional risk minimization activities, a statement that the safety information in the product information of the generic product is aligned with the originator product is sufficient for RMP part V. Where new risks have been identified for the generic product, the risk minimization activities for such safety concerns should be presented in part V, following the same elements as for a full marketing authorization application.

If the originator product does have additional risk minimization activities, a full part V is required for the generic product.

- RMP part VI: The elements are the same as for a full initial marketing authorization application, to the extent of data requested and provided in other parts of the RMP, as per above.
- RMP part VII: The elements are the same for a full initial marketing authorization application. For RMP annexes 4 and 5, the applicant is strongly encouraged to use materials as similar, in content, as possible to the originator product.

In the case of initial marketing authorization application of a new generic product of a non-SFDA registered reference product, the following RMP parts should be submitted:

- RMP part I: The elements are the same as for a full initial marketing authorization application.
- RMP part II: Only RMP modules SVII and SVIII might be applicable. The applicant is required to justify the proposed safety concerns, or the lack of any thereof, using available evidence from published scientific literature.
- RMP parts III-VII: The elements are the same as for a full initial marketing authorization application.

V.C.1.1.2. New applications, i.e. "informed consent"

The RMP should be the same as the RMP of the cross-referred medicinal product. An RMP will still be required even if the cross-referred product does not have an RMP. If the marketing

authorization holder is the same as for the authorized product, the marketing authorization holder is encouraged to put in place only one RMP document for their products with the same active substance.

V.C.1.1.3. New applications, i.e. "hybrid"

The RMP elements are the same as for a generic product. However, for changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, the applicant should discuss in RMP module SVII whether this results in the addition or deletion of a safety concern. Clinical trial data generated to support the application should be discussed in the RMP, as appropriate (e.g. RMP part II, modules SI, SIII). Other parts of the RMP should also be aligned (e.g. parts V and VI).

V.C.1.1.4. New applications, i.e. involving "fixed combination"

There are two situations:

1. The combination contains a new active substance: A full RMP, following the elements as for full initial marketing authorization application, should be submitted. RMP modules SI-SVI should focus on the new active substance.

2. The combination does not contain a new active substance: The RMP should follow the elements for a generic product. For the purpose of establishing the elements of RMP part II, "the originator product" should be read as "any/all authorized products containing the same active substances included in the new product".

In addition, new data generated with the fixed combination should be provided in modules SII and SIII.

V.C.1.1.5. New applications, i.e. "well established medicinal use"

The elements are as follows:

- RMP part I: The elements are the same as for a full initial marketing authorization application.
- RMP part II: Only RMP modules SVII and SVIII might be applicable. The applicant is required to justify the proposed safety concerns, or the lack of any thereof, using available evidence from published scientific literature.
- RMP parts III-VII: The elements are the same as for a full initial marketing authorization

application.

V.C.1.1.6. New applications, i.e. “biosimilar products”

For new applications for biosimilar products, the RMP elements are described in GVP P. II.

V.C.1.2. Risk management plans first submitted post-authorization

V.C.1.2.1. New risk management plans at the request of the SFDA to address one or more safety concerns

The elements are the same as those applicable to a generic product where the originator product does not have an RMP (see V.C.1.1.1.).

Two possible scenarios are envisaged:

1. MAHs may be requested to submit an RMP with an RMP module SVII focused on the safety concern(s) evaluated in the procedure. Other safety concerns should be included as needed.
2. MAHs may be requested to submit an RMP based on a comprehensive identification of safety concerns.

It is left to the discretion of the SFDA, which is the most appropriate in given circumstances.

V.C.1.2.2. Unsolicited risk management plan submission in post-authorization phase

This RMP follows the elements of the type of marketing authorization under which this medicinal product was initially submitted (i.e. full marketing authorization application, generic medicinal products, “informed consent” applications, etc., see V.C.1.1.).

V.C.2. Submission of a risk management plan to the SFDA

Currently, for authorized products, the RMP is submitted as PDF files within the eCTD/CTD submission. Following a decision where the procedure has involved the submission of an RMP, MAHs should submit the RMP annex I in XML format. RMP annex I provides the key information regarding the RMP in a structured electronic format. Hence, this annex should be submitted only upon request from the SFDA.

The initial RMP should be submitted as part of the initial marketing authorization, or if required, for those products that do not have an RMP, through the appropriate post-

authorization procedure.

V.C.2.1. Risk management plans updates

An RMP update including the Saudi-Specific Annex (SSA) (see V.B.10.9.) is expected to be submitted at any time when there is a change in the list of the safety concerns, or when there is a new or a significant change in the existing additional pharmacovigilance or additional risk minimization activities. The significant changes of the existing additional pharmacovigilance and risk minimization activities may include removing such activities from the RMP. For example, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials would be expected to be reflected in an updated RMP with the procedure triggering those changes.

An update of the RMP might be considered when data submitted in the procedure results or is expected to result in changes of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection activities, or of routine risk minimization activities recommending specific clinical measures to address the risk. For example, a change in study objectives, population or due date of final results, or addition of a new safety concern in the key messages of the educational materials would be expected to be reflected in an updated RMP with the procedure triggering those changes.

An update of the RMP might be considered when data submitted in the procedure results or is expected to result in changes of routine pharmacovigilance activities beyond adverse reaction reporting and signal detection activities, or of routine risk minimisation activities recommending specific clinical measures to address the risk. For example, an RMP update might also be warranted with a significant change of the plans for annual enhanced safety surveillance (routine pharmacovigilance activity), or when monitoring of renal function is added as a recommendation in the Special warnings and precautions for use section 4.4 of the SPC (routine risk minimization activity). The need to update the plans to evaluate the effectiveness of risk minimization activities should also be considered with such updates.

When an emerging safety issue is still under assessment (as defined in GVP Module VI), in particular in the context of a signal or potential risk that could be an important identified risk, an RMP update may be required if the emerging safety issue is confirmed and the important identified or potential risk requires to be added to the list of safety concerns in the

RMP.

Unless requested otherwise, a track-changes RMP document should be included with every RMP update, showing changes introduced in the latest update (as applicable), as well as compared with the "current" approved version of the RMP.

A medicinal product can only have one "current" approved version of an RMP. If several updates to the RMP are submitted during the course of a procedure, the version considered as the "current" approved RMP for future updates and track-changes purposes shall be the one submitted with the closing sequence of the procedure.

When an RMP update is submitted with a procedure, the RMP is considered approved at the end of the procedure, when all changes are considered acceptable.

RMP management with parallel procedures

If a medicinal product has more than one concurrently on-going procedure which requires submission of an RMP, ideally a combined RMP should be submitted with appropriate separation of data in RMP module SIII. The best regulatory path for the RMP update in case of multiple procedures potentially impacting on the RMP content should be discussed with the SFDA before submission.

RMP updates with the PSUR/PBRER

If, when preparing a PSUR/PBRER, there is a need for changes to the RMP as a result of new safety concerns, or other data presented in the PSUR/PBRER, then an updated RMP should be submitted at the same time. In this case no stand-alone RMP variation is necessary. Should only the timing for submission of both documents coincide, but the changes are not related to each other, then the RMP submission should be handled as a stand-alone variation. MAHs should take the opportunity of another upcoming procedure to update their RMP. Alternatively, MAHs should submit a separate variation to update their RMP.

MODULE VI – COLLECTION, MANAGEMENT AND SUBMISSION OF REPORTS OF SUSPECTED ADVERSE REACTIONS TO MEDICINAL PRODUCTS

VI.A. INTRODUCTION

This Module addresses the legal requirements by SFDA, as regards the collection, data management and submission of individual reports of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorized in the KSA.

The guidance provided in this Module does not address the collection, management and reporting of events or patterns of use, which do not result in suspected adverse reactions (e.g. asymptomatic overdose, abuse, off-label use, misuse or medication error) or which do not require to be reported as ICSR. This information may however need to be collected and presented in PSUR/PBRERs for the interpretation of safety data or for the benefit risk evaluation of medicinal products. With regard to this, guidance provided in Module VII applies.

VI.A.1. Definitions

General principles presented in the ICH-E2A and ICH-E2D guidelines should be adhered to; some of these principles included as well in this chapter.

VI.A.1.1 Adverse reaction, causality

An **adverse reaction** is defined as a response to a medicinal product, which is noxious and unintended.

- Adverse reactions may arise from the use of a medicinal product within the terms of the marketing authorization, from occupational exposure, or use outside the terms of the marketing authorization, including overdose, off-label use, misuse, abuse and medication errors;

VI.A.1.1.1. Causality

In accordance with the ICH-E2A guideline, the definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. For regulatory reporting purposes, as detailed in the ICH-E2D guideline, if an event is

spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse reaction. Therefore, all spontaneous reports notified by healthcare professionals, patients or consumers are considered suspected adverse reactions, since they convey the suspicions of the primary sources, unless the reporters specifically state that they believe the events to be unrelated or that a causal relationship can be excluded.

VI.A.1.1.2.Overdose, off-label use, misuse, abuse, occupational exposure

a. **Overdose**

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.

b. **Off-label use**

This relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorized product information.

c. **Misuse**

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorized product information.

d. **Abuse**

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

e. **Occupational exposure**

This refers to the exposure to a medicinal product, as a result of one's professional or non-professional occupation.

VI.A.1.2. Medicinal product

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

The scope of this module is not only applicable to medicinal products authorized in the KSA but also to any such medicinal products commercialized outside the KSA by the same MAH (see VI.C.2.2). Given that a medicinal product is authorized with a defined composition, all the adverse reactions suspected to be related to any of the active substances being part of a medicinal product authorized in the KSA should be managed in accordance with the requirements presented in this module. This is valid independently of the strengths, pharmaceutical forms, routes of administration, presentations, authorized indications, or trade names of the medicinal product.

The guidance provided in this Module also applies, subject to amendments where appropriate, to medicinal products supplied in the context of compassionate use.

VI.A.1.3. Primary source

The primary source of the information on a suspected adverse reaction(s) is the person who reports the facts. Several primary sources, such as healthcare professionals and/or a consumer, may provide information on the same case. In this situation, all the primary sources' details, including the qualifications, should be provided in the case report, with the "Primary source(s)" section repeated as necessary in line with the ICH-E2B guideline.

In accordance with the ICH-E2D

- A healthcare professional is defined as a medically-qualified person such as physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations; and
- A consumer is defined as a person who is not a healthcare professional such as a patient, lawyer, friend, relative of a patient or carer.

VI.A.1.4. Medical confirmation

Medical documentations (e.g. laboratory or other test data) provided by a consumer that support the occurrence of the suspected adverse reaction, or which indicate that an identifiable healthcare professional suspects a reasonable possibility of causal relationship between a medicinal product and the reported adverse event, are sufficient to consider the spontaneous report as confirmed by a healthcare professional.

If a consumer initially reports more than one reaction and at least one receives medical confirmation, the whole report should be documented as a spontaneous report confirmed by a healthcare professional and be reported accordingly. Similarly, if a report is submitted by a

medically qualified patient, friend, relative of the patient or carer, the case should also be considered as a spontaneous report confirmed by a healthcare professional.

VI.A.1.5 Seriousness

As described in the ICH-E2A guideline, a serious adverse reaction corresponds to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly/birth defect.

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

Medical judgement should be exercised in deciding whether other situations should be considered as serious reactions. Some medical events may jeopardize the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered as serious (examples are provided in Section II.B of ICH E2A guideline). The EudraVigilance Expert Working Group has coordinated the development of an important medical event (IME) terms list based on the Medical Dictionary for Regulatory Activities (MedDRA). This IME list aims to facilitate the classification of suspected adverse reactions, the analysis of aggregated data and the assessment of the ICSRs in the framework of the day-to-day pharmacovigilance activities.

VI.A.1.6. Individual Case Safety Report (ICSR)

This 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. A valid ICSR should include at least one identifiable reporter, one single identifiable patient, at least one suspect adverse reaction and at least one suspect medicinal product.

VI.B. STRUCTURES AND PROCESSES

Section B of this Module highlights the general principles in relation to the collection, recording and reporting of reports of suspected adverse reactions associated with medicinal products for human use, which are applicable to the SFDA. The definitions and recommendations provided in VI.A should be followed.

VI.B.1. Collection of individual safety reports

MAHs should act appropriately in order to collect and collate all reports of suspected adverse reactions associated with medicinal products for human use originating from unsolicited or solicited sources.

For this purpose, a pharmacovigilance system should be developed to allow the acquisition of sufficient information for the scientific evaluation of those reports.

The system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment.

All notifications that contain pharmacovigilance data should be recorded and archived in compliance with the applicable data protection requirement in Saudi Arabia.

The system should also be structured in a way that allows for reports of suspected adverse reactions to be validated (see VI.B.2) in a timely manner and exchanged between the SFDA and MAHs within the legal reporting time frame (see VI.B.7.1).

In accordance with the ICH-E2D guideline, two types of safety reports are distinguished in the post-authorization phase; reports originating from unsolicited sources and those reported as solicited.

VI.B.1.1. Unsolicited reports

VI.B.1.1.1. Spontaneous reports

A spontaneous report is an unsolicited communication by a healthcare professional, or consumer to the SFDA or the MAH that describes one or more suspected adverse reactions in a patient who was given one or more medicinal products and that does not derive from a study or any organized data collection systems where adverse events reporting is actively sought, as defined in VI.B.1.2. With regard to this, the following situations should also be considered as spontaneous reports:

- Stimulated reporting that occurs consequent to a “Direct Healthcare Professional Communication”, publication in the press, questioning of healthcare professionals by company representatives, communication from patients’ organizations to their members, or class action lawsuits;

- Unsolicited consumer adverse reactions reports should be handled as spontaneous reports irrespective of any subsequent “medical confirmation”.

The reporting modalities and applicable time frames for spontaneous reports are described in VI.B.7 and VI.B.8.

VI.B.1.1.2. Literature reports

The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the benefit-risk balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. MAHs are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. The MAH should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties. In addition, MAHs should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorization, and to bring them to the attention of the company safety department as appropriate.

Reports of suspected adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed and assessed by MAHs to identify and record ICSRs.

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

Valid ICSRs should be reported according to the modalities detailed in VI.B.7 and VI.B.8.

One case should be created for each single patient identifiable based on characteristics provided in VI.B.2. Relevant medical information should be provided, and the publication author(s) should be considered as the primary source(s).

KSA’s specific requirements, as regards medicinal products and scientific and medical publications, which are not monitored by the SFDA and for which valid ICSRs shall be reported by MAHs.

VI.B.1.1.3. Reports from non-medical sources

If a MAH becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be handled as a spontaneous report. Every attempt should be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR. The same reporting time frames should be applied as for other spontaneous reports.

VI.B.1.1.4. Information on suspected adverse reactions from the internet or digital media

MAHs should regularly screen internet or digital media (Although not exhaustive, the following list should be considered as digital media: web site, web page, blog, vlog, social network, internet forum, chat room and health portal.) under their management or responsibility, for potential reports of suspected adverse reactions. In this aspect, digital media is considered to be company sponsored if it is owned, paid for and/or controlled by the MAH. The frequency of the screening should allow for potential valid ICSRs to be reported to the SFDA within the appropriate reporting timeframe based on the date the information was posted on the internet site/digital medium. MAHs may also consider utilizing their websites to facilitate the collection of reports of suspected adverse reactions.

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

Unsolicited cases of suspected adverse reactions from the internet or digital media should be handled as spontaneous reports. The same reporting time frames as for spontaneous reports should be applied (see VI.B.7).

In relation to cases from the internet or digital media, the identifiability of the reporter refers to the existence of a real person, that is, it is possible to verify the contact details of the reporter (e.g., an email address under a valid format has been provided). If the country of the primary source is missing, the country where the information was received, or where the review took place, should be used as the primary source country.

VI.B.1.2. Solicited reports

As defined in ICH-E2D guideline, solicited reports of suspected adverse reactions are those derived from organized data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, compassionate use or name patient use, or information gathering on efficacy or patient compliance. Adverse reactions reports obtained from any of these data collection systems should not be considered spontaneous. This is with the exception of suspected adverse reactions originating from non-interventional post-authorization studies related to specified adverse events for which the protocol does not require their systematic collection or reports of suspected adverse reactions from compassionate use or named patient use where the systematic collection of adverse events in these programs is not required.

With regard to the submission as ICSRs, solicited reports should be classified as study reports, and should have an appropriate causality assessment, to consider whether they refer to suspected adverse reactions and therefore meet validation criteria (see VI.B.2. for ICSRs validation).VI.B.2. Validation of reports

Only valid ICSRs qualify for reporting. All reports of suspected adverse reactions should therefore be validated before reporting them to the SFDA to make sure that the minimum criteria for reporting are included in the reports (ICH-E2D guideline). These are:

- **One or more identifiable reporter** ((see VI.A.1.4 for primary source definition), characterized by parameters such as qualification (e.g. physician, pharmacist, other healthcare professional, consumer or other non-healthcare professional) name, initials or address. Whenever possible, contact details for the reporter should be recorded so that follow-up activities can be performed. However, if the reporter does not wish to provide contact details, the ICSR should still be considered as valid providing the organization who was informed of the case was able to confirm it directly with the reporter. All parties providing case information or approached for case information should be identifiable, not only the initial reporter.

- **One single identifiable patient**, characterized by at least one of the following qualifying descriptors: initials, patient identification number, date of birth, age, age group or gender. The information should be as complete as possible.

- **One or more suspected substance/medicinal product** (see VI.A.1.3. for definition).

- **One or more suspected adverse reaction (see VI.A.1.1).** If the primary source has made an explicit statement that a causal relationship between the medicinal product and the adverse event has been excluded and the receiver (the SFDA or MAH) agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete. The report does not also qualify as a valid ICSR if it is reported that the patient experienced an unspecified adverse reaction and there is no information provided on the type of adverse reaction experienced. Similarly, the report is not valid if only an outcome (or consequence) is notified and (i) no further information about the clinical circumstances is provided to consider it as a suspected adverse reaction, or (ii) the primary source has not indicated a possible causal relationship with the suspected medicinal product. For instance, a MAH is made aware that a patient was hospitalized or died, without any further information. In this particular situation, medical judgement should always be applied in deciding whether the notified information is an adverse reaction or an event. For example, a report of sudden death would usually need to be considered as a case of suspected adverse reaction and reported.

The lack of any of these four elements means that the case is considered incomplete and does not qualify for submission as ICSR. MAHs are expected to exercise due diligence in following up the case to collect the missing data elements. Reports, for which the minimum information is incomplete, should nevertheless be recorded within the pharmacovigilance system for use in on-going safety evaluation activities. Recommendations on the electronic reporting of valid ICSRs, when missing information has been obtained are provided in VI.C.6.2.2.8.

When collecting reports of suspected adverse reactions via the internet or digital media, the term “identifiable” refers to the possibility of verification of the existence of a reporter and a patient (see VI.B.1.1.4).

When a MAH is made aware that the primary source may also have reported the suspected adverse reaction to another concerned party, the report should still be considered as a valid ICSR. All the relevant information necessary for the detection of the duplicate case should be included in the ICSR (For further guidance on reporting of other duplicate ICSRs, refer to Section A.1.11 “Other case identifiers in previous transmission” of ICH-E2B (R2).

A valid case of suspected adverse reaction initially submitted by a consumer cannot be downgraded to a report of non-related adverse event if the contacted healthcare professional (nominated by the consumer for follow-up information) disagrees with the consumer's suspicion (see VI.A..1.1). In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR. Guidance on the reporting of the medical confirmation of a case, provided in ICH-E2B(R2) guideline Section A.1.14 ("Was the case medically confirmed, if not initially from a healthcare professional?"), should be followed.

For solicited reports of suspected adverse reactions (see VI.B.1.2), where the receiver disagrees with the reasonable possibility of causal relationship between the suspected medicinal product and the adverse reaction expressed by the primary source, the case should not be downgraded to a report of non-related adverse event. The opinions of both, the primary source and the receiver, should be recorded in the ICSR. The same principle applies to the ICSR seriousness criterion, which should not be downgraded from serious to non-serious if the receiver disagrees with the seriousness reported by the primary source.

VI.B.2. 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 (see VI.B.2 for ICSRs validation). Any attempt to obtain follow-up information should be documented.

Follow-up methods should be tailored towards optimizing the collection of missing information. This should be done in ways that encourage the primary source to submit new information relevant for the scientific evaluation of a particular safety concern. The use of targeted specific forms in the local language should avoid requesting the primary source to repeat information already provided in the initial report and/or to complete extensive questionnaires, which could discourage future spontaneous reporting. Therefore, consideration should be given to pre-populating some data fields in those follow-up report forms to make their completion by the primary source easy.

When information is received directly from a consumer suggesting that an adverse reaction may have occurred, if the information is incomplete, attempts should be made to obtain consent to contact a nominated healthcare professional to obtain further follow-up information. When such a case, initially reported by a consumer, has been confirmed (totally or partially) by a healthcare professional, this information should be clearly highlighted in the ICSR (For further guidance on reporting this information, refer to ICH-E2B (R2)).

For suspected adverse reactions relating to biological medicinal products, the definite identification of the concerned product with regard to its manufacturing is of particular importance. Therefore, all appropriate measures should be taken to clearly identify the name of the product and the batch number.

VI.B.3. Data management

Electronic data and paper reports of suspected adverse reactions should be stored and treated in the same way as other medical records with appropriate respect for confidentiality regarding patients' and reporters' identifiability and in accordance with local data privacy laws. Confidentiality of patients' records including personal identifiers, if provided, should always be maintained. Identifiable personal details of reporting healthcare professionals should be kept in confidence. Concerning patient's and reporter's identifiability, case report information should be transmitted between stakeholders (MAHs or the SFDA) in accordance with local data privacy laws (see VI.C.6.2.2.8 for the processing of personal data in ICSRs).

In order to ensure pharmacovigilance data security and confidentiality, strict access controls should be applied to documents and to databases to authorized personnel only. This security extends to the complete data path. In this aspect, procedures should be implemented to ensure security and non-corruption of data during data transfer.

When transfer of pharmacovigilance data occurs within an organization or between organizations having concluded contractual agreements, the mechanism should be such that there is confidence that all notifications are received; in that, a confirmation and/or reconciliation process should be undertaken.

Correct data entry, including the appropriate use of terminologies, should be verified by quality assurance auditing, either systematically or by regular random evaluation. Data entry staff should be instructed in the use of the terminologies, and their proficiency confirmed.

Data received from the primary source should be treated in an unbiased and unfiltered way

and inferences as well as imputations should be avoided during data entry or electronic transmission. The reports should include the verbatim text as used by the primary source or an accurate translation of it. The original verbatim text should be coded using the appropriate terminology as described in VI.B.8. In order to ensure consistency in the coding practices, it is recommended to use, where applicable, the translation of the terminology in the local language to code the verbatim text.

Electronic data storage should allow traceability (audit trail) of all data entered or modified, including dates and sources of received data, as well as dates and destinations of transmitted data.

A procedure should be in place to account for identification and management of duplicate cases at data entry and during the generation of aggregated reports (see VI.C.6.2.4).

VI.B.4. Quality management

MAHs should have a quality management system in place to ensure compliance with the necessary quality standards at every stage of case documentation, such as data collection, data transfer, data management, data coding, case validation, case evaluation, case follow-up, ICSR reporting and case archiving (see VI.C.6.2.4 and Module I). Conformity of stored data with initial and follow-up reports should be verified by quality control procedures, which permit for the validation against the original data or images thereof. In this aspect, the source data (e.g., letters, emails, records of telephone calls that include details of an event) or an image of the source data should be easily accessible.

Clear written standard operating procedures should guarantee that the roles and responsibilities and the required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system. This is equally applicable to activities that are contracted out to third parties, whose procedures should be reviewed to verify that they are adequate and compliant with applicable requirements.

Staff directly performing pharmacovigilance activities, should be appropriately trained in applicable pharmacovigilance legislation and guidelines in addition to specific training in report processing activities for which they are responsible and/or undertake. Other personnel who may receive or process safety reports (e.g. clinical development, sales, medical information, legal, quality control) should be trained in adverse event collection and reporting in accordance with internal policies and procedures.

VI.B.5. Special situations

VI.B.5.1. Use of a medicinal product during pregnancy or breastfeeding

a. Pregnancy

Reports, where the embryo or fetus may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure), should be followed-up in order to collect information on the outcome of the pregnancy and development of the child after birth. When an active substance (or one of its metabolites) has a long half-life, this should be considered when assessing the possibility of exposure of the embryo, if the medicinal product was taken before conception.

Not infrequently, pregnant women or healthcare professionals will contact MAHs to request information on the teratogenicity of a medicinal product and/or experience of use during pregnancy. Reasonable attempts should be made to obtain information on any possible medicinal product exposure to an embryo or fetus and to follow-up on the outcome of the pregnancy.

Reports of exposure to medicinal products during pregnancy should contain as many detailed elements as possible in order to assess the causal relationships between any reported adverse events and the exposure to the suspected medicinal product. In this context the use of standard structured questionnaires is recommended.

Individual cases with an abnormal outcome associated with a medicinal product following exposure during pregnancy are classified as serious reports and should be reported, in accordance with the requirements outlined in VI.B.7.

This especially refers to:

- Reports of congenital anomalies or developmental delay, in the fetus or the child;
- Reports of fetal death and spontaneous abortion; and
- Reports of suspected adverse reactions in the neonate that are classified as serious.

Other cases, such as reports of induced termination of pregnancy without information on congenital malformation, reports of pregnancy exposure without outcome data or reports which have a normal outcome, should not be reported since there is no suspected adverse reaction. These reports should however be collected and discussed in the PSUR/PBRERs (See Module VII).

However, in certain circumstances, reports of pregnancy exposure with no suspected reactions may necessitate to be reported. This may be a condition of the marketing authorization or stipulated in the RMP; for example, pregnancy exposure to medicinal products contraindicated in pregnancy or medicinal products with a special need for surveillance because of a high teratogenic potential (e.g. thalidomide, isotretinoin).

A signal of a possible teratogen effect (e.g. through a cluster of similar abnormal outcomes) should be notified immediately to the SFDA in accordance with the recommendations presented in VI.C.2.1.6.

b. Breastfeeding

Suspected adverse reactions which occur in infants following exposure to a medicinal product from breast milk should be reported in accordance with the criteria outlined in VI.B.7. (Council for International Organizations of Medical Sciences (CIOMS). Definition and application of terms of vaccine pharmacovigilance (report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance). Genève: CIOMS; 2012. http://www.cioms.ch/).

VI.B.5.2. Use of a medicinal product in a pediatric or elderly population

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

VI.B.5.3. Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure

For the purpose of this Module, medication error refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the healthcare professional, patient or consumer.

Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure with no associated adverse reaction should not be reported as ICSRs. They should be considered in PSUR/PBRERs as applicable. When those reports constitute safety issues impacting on the benefit-risk balance of the medicinal product, they should be notified to the SFDA in accordance with the recommendations provided in VI.C.2.1.6.

Reports associated with suspected adverse reactions should be subject to reporting in

accordance with the criteria outlined in VI.B.7 and with the electronic reporting requirements described in VI.C.6.2.3.3. They should be routinely followed-up to ensure that the information is as complete as possible with regards to the symptoms, treatments, outcomes, context of occurrence (e.g., error in prescription, administration, dispensing, dosage, unauthorized indication or population, etc.).

VI.B.5.4. Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy should be recorded and followed-up if incomplete. They should normally report within a 15-day time frame (See VI.C.3.as regards electronic reporting in the KSA) but should also be discussed in PSUR/PBRERs as applicable. This applies unless the reporter has specifically stated that the outcome was due to disease progression and was not related to the medicinal product.

Clinical judgement should be used when considering if other cases of lack of therapeutic efficacy qualify for reporting. For example, an antibiotic used in a life-threatening situation where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, a life-threatening infection, where the lack of therapeutic efficacy appears to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible, should be reported within 15 days.

For vaccines, cases of lack of therapeutic efficacy should be reported, in particular with the view to highlight potential signals of reduced immunogenicity in a sub-group of vaccines, waning immunity, or strain replacement. With regard to the latter, it is considered that spontaneously reported cases of lack of therapeutic efficacy by a healthcare professional may constitute a signal of strain replacement. Such a signal may need prompt action and further investigation through post-authorization safety studies as appropriate. General guidance regarding the monitoring of vaccines failure, provided in the Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance may be followed.

VI.B.6. Reporting of ICSRs

Only valid ICSRs (see VI.B.2) should be reported. 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 the SFDA or of any personnel of the MAH, including medical representatives and contractors. This date should be considered as day zero. In practice, this

is the first business day the receiver becomes aware of the information.

Where the MAH has set up contractual arrangements with a person or an organization, explicit procedures and detailed agreements should exist between the MAH and the person/organization to ensure that the MAH can comply with the reporting obligations. These procedures should in particular specify the processes for exchange of safety information, including timelines and regulatory reporting responsibilities and should avoid duplicate reporting to the SFDA.

For ICSRs described in the scientific and medical literature (See VI.B.1.1.2), the clock starts (day zero) with awareness of a publication containing the minimum information for reporting. Where contractual arrangements are made with a person/organization to perform literature searches and/or report valid ICSRs, detailed agreements should exist to ensure that the MAH can comply with the reporting obligations.

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. For the purpose of reporting, 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. See also VI.C.6.2.2.7 as regards the distinction between significant and non-significant follow-up information.

VI.B.6.1. Reporting time frames of ICSRs

In general, the reporting of serious valid ICSRs is required as soon as possible, but in no case later than 15 calendar days after initial receipt of the information by the national or regional pharmacovigilance center of the SFDA or by any personnel of the MAH, including medical representatives and contractors. This applies to initial and follow-up information. Where a case initially reported as serious becomes non-serious, based on new follow-up information, this information should still be reported within 15 days; the reporting time frame for non-serious reports should then be applied for the subsequent follow-up reports.

Information as regards the reporting time frame of non-serious valid ICSRs in the KSA is provided in VI.C.3.

VI.B.7. Reporting modalities

Considering the international dimension of adverse reactions reporting and the need to achieve harmonization and high quality between all involved parties, ICSRs should be submitted electronically as structured data with the use of controlled vocabularies for the relevant data elements where applicable. In this aspect, with regard to the content and format of electronic ICSRs, MAHs should adhere to the following internationally agreed ICH guidelines and standards:

- ICH M1 terminology - Medical Dictionary for Regulatory Activities (MedDRA);
- MedDRA Term Selection: Points to Consider Document - The latest version of the ICH-endorsed Guide for MedDRA Users;
- ICH M2 EWG - Electronic Transmission of Individual Case Safety Reports Message Specification;
- ICH E2B(R2) - Maintenance of the ICH Guideline on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports;
- ICH E2B Implementation Working Group - Questions & Answers (R5) (March 3, 2005);

As technical standards evolve over time, the above referred documents may require revision and maintenance. In this context, the latest version of these documents should always be considered.

Information regarding KSA specific reporting modalities is provided in VI.C.4.

VI.C. OPERATION WITHIN KSA

Section C of this Module highlights the SFDA 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 the KSA.

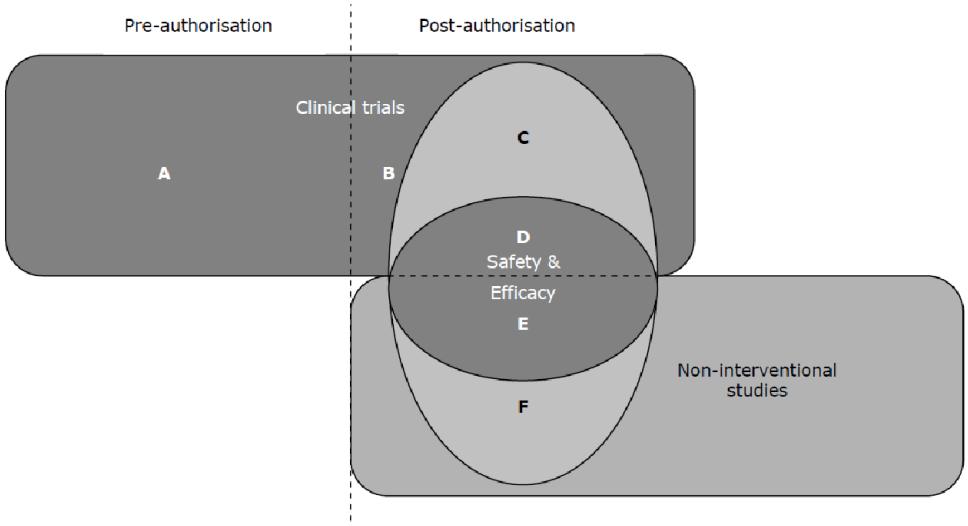
VI.C.1. Management of individual safety reports for clinical trials and post authorization studies in the KSA

Post-authorization safety or efficacy studies requested by the SFDA, or conducted voluntarily by MAHs, can either be clinical trials or non-interventional studies as shown in Figure VI.1. Further guidance on post-authorization safety studies is provided in Module VIII.

The different types of studies and clinical trials which can be conducted in the KSA are illustrated in Figure VI.1. The reporting rules of solicited reports of suspected adverse

reactions to the NPC database modules are dependent on the types of organized collection systems where they occurred; recommendations provided in VI.C.6.2.1 should be followed.

Figure VI.1. Diagram illustrating different types of clinical trials and studies in the EU



Section A: Clinical trials which are conducted when no marketing authorization exists in the KSA.

Section B: Clinical trials, which are conducted in the post-authorization period, e.g. for new indication.

Section C: Post-authorization clinical trials conducted in accordance with the SPC indication and condition of use.

Section D: Post-authorization safety or efficacy clinical trials requested by SFDA or conducted voluntarily by MAHs, due to the nature of the intervention.

Section E: Non-interventional post-authorization safety or efficacy studies requested or conducted voluntarily by the MAHs and which follow the same legal requirements.

Section F: Non-interventional post-authorization studies conducted in accordance with SPC indication and condition of use.

VI.C.1.1. Management of individual safety reports of clinical trials

A suspected adverse reaction to an investigational medicinal product occurring in a clinical trial. It is therefore excluded from the scope of this Module even if the clinical trial where the suspected adverse reaction occurred is a post-authorization safety or efficacy study or conducted voluntarily.

If a clinical trial, yields safety concerns which impact on the benefit-risk balance of an

authorized medicinal product, the SFDA where the medicinal product is authorized and the SFDA should be notified immediately in accordance with the modalities detailed in VI.C.2.1.6. This applies as well if a safety concern arises from a clinical trial conducted exclusively outside the KSA.

The safety data from clinical trials to be presented in the relevant sections of the PSUR/PBRER of the authorized medicinal product are detailed in Module VII.

VI.C.1.2. Management of individual safety reports for non-interventional post-authorization studies, compassionate use and named patient use

Post-authorization studies include non-interventional post-authorization studies, compassionate use, named patient use, other patient support and disease management programs, registries, surveys of patients or healthcare providers, and information gathering on efficacy or patient compliance. They may involve the receipt of information on adverse events.

The SFDA and MAHs should have in place a system to collect full and comprehensive case information and to evaluate that information in order to determine whether the collected adverse events are possibly related to the studied (or supplied) medicinal product and should be classified and processed as ICSRs of suspected adverse reactions.

Different methods may be applied for assessing the causal role of a medicinal product on the reported adverse event (e.g. WHO-UMC system for standardized case causality assessment). In this situation, the levels of causality, which correspond to a reasonable possibility of causal relationship, should be established in advance in order to determine when an adverse event is considered as an adverse reaction.

Only valid ICSRs (See VI.B.2) of adverse reactions, which are suspected to be related to the studied (or supplied) medicinal product by the primary source or the receiver of the case, should be reported. They should be considered as solicited reports (with the exception of certain reports from compassionate use or named patient use (See VI.C.1.2.2)) and reported by MAHs.

It may happen that reports of adverse reactions are only suspected to be related to other medicinal products which are not subject to the scope of the post-authorization study. If there is no interaction with the studied (or supplied) medicinal product, these reports should be notified by the primary source, to the SFDA where the reaction occurred or to the MAH of

the suspected medicinal product, but not to both to avoid duplicate and while respecting the electronic reporting recommendations detailed in VI.C.6.2.

Further guidance on post-authorization studies conducted by MAHs is provided in VI.C.2.1.2.

Academic sponsors should follow local requirements as regards the reporting of cases of suspected adverse reactions to the SFDA where the reaction occurred. However, where a study is directly financed, or where the design is influenced by a MAH, the MAH should fulfil the reporting requirements detailed in this Module.

VI.C.1.2.1. Non-interventional studies

- Non-interventional studies should be distinguished between those with primary data collection directly from consumers and healthcare professionals, and study designs, which are based on secondary use of data such as studies based on medical chart reviews or electronic healthcare records, systematic reviews or meta-analyses.
- Non-interventional studies with primary data collection directly from patients and healthcare professionals should be considered as organized data collection systems where adverse events are actively sought. Only reports of adverse reactions suspected to be related to the studied medicinal product should be reported. Reports of adverse events should only be summarized in the study report, where applicable.
- For non-interventional study designs, which are based on secondary use of data, adverse reactions reporting is not required. Reports of adverse events/reactions should only be summarized in the study report, where applicable.
- In case of doubt, the reporting requirement should be clarified with the SFDA.
- With regard the reporting of cases of suspected adverse reactions to local ethics committees and investigators, the national legislation should be followed as applicable.

VI.C.1.2.2. Compassionate use, named patient use

Where an organization is notified or becomes aware of an adverse event, it should be managed as followed depending on the requirements in the SFDA:

- For compassionate and named patient uses where adverse events are actively sought, only reports of adverse reactions suspected to be related to the supplied medicinal product should be reported. They should be considered as solicited reports.

- For compassionate and named patient uses where the reporting of adverse events is not solicited, any notified noxious or unintended response to the supplied medicinal product should be considered as a spontaneous report of suspected adverse reaction by the receiver of the case.

VI.C.2. Collection of individual safety reports

VI.C.2.1. MAHs responsibilities

Each MAH shall have in place a system for the collection and recording of all reports of suspected adverse reactions, which are brought to its attention, whether reported spontaneously by healthcare professionals or consumers or occurring in the context of a post-authorization study.

MAHs shall establish mechanisms enabling the traceability and follow-up of adverse reaction reports while complying with the data protection legislation. 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 ceased to exist. However, the documents shall be retained for a longer period where SFDA law so requires.

With regard to the collection and recording of reports of suspected adverse reactions, MAHs responsibilities apply to reports related to medicinal products (see VI.A.1.2) for which ownership cannot be excluded on the basis of one the following criteria: medicinal product name, active substance name, pharmaceutical form, batch number or route of administration.

The MAH shall ensure that any information on adverse reactions, suspected to be related to at least one of the active substances of its medicinal products authorized in the KSA, is brought to its attention by any company outside the KSA belonging to the same mother company (or group of companies). The same applies to the MAH when having concluded a commercial agreement with a company outside the KSA for one of its medicinal products authorized in the KSA. The clock for reporting tarts when a valid ICSR is first received by one of these companies outside the KSA.

In addition to the requirements presented in this chapter, the general principles detailed in Section VI.B, together with the reporting modalities presented in VI.C.3, VI.C.4 and VI.C.6 should be applied by MAHs to all reports of suspected adverse reactions.

VI.C.2.1.1. Spontaneous reports

MAHs shall record all reports of suspected adverse reactions originating from or outside the KSA, which are brought to their attention spontaneously by healthcare professionals, or consumers. This includes reports of suspected adverse reactions received electronically or by any other appropriate means. MAHs must have an Arabic webpage included the communication channels with the local QPPV. In this context, MAHs may consider utilizing their webpage to facilitate the collection of reports of suspected adverse reactions by providing adverse reactions forms for reporting, or appropriate contact details for direct communication (See VI.B.1.1.4).

VI.C.2.1.2. Solicited reports

MAHs shall record all reports of suspected adverse reactions originating from or outside the KSA, which occur in post-authorization studies, initiated, managed, or financed by them. General guidance on post-authorization studies is provided in VI.C.1.2. Electronic reporting recommendations for cases originating in post-authorization studies are detailed in VI.C.6.2.2.7.

For post authorization studies, MAHs should have mechanisms in place to collect full and comprehensive case information and to evaluate that information, in order to allow meaningful assessment of individual cases and reporting of valid ICSRs (See VI.B.2) related to the studied (or supplied) medicinal product. MAHs should therefore exercise due diligence in establishing such system, in following-up those reports (See VI.B.3) and in seeking the view of the primary source as regard the causal role of the studied (or supplied) medicinal product on the notified adverse event. Where this opinion is missing, the MAH should exercise its own judgement based on the information available in order to decide whether the report is a valid ICSR, which should be reported to the SFDA. This does not apply to study designs based on secondary use of data for which reporting of ICSRs is not required (See VI.C.1.2.1).

Safety data to be presented in the relevant sections of the PSUR/PBRER of the authorized medicinal product are detailed in Module VII.

VI.C.2.1.3. Case reports published in the scientific and medical literature

General principles in relation to the monitoring for individual cases of suspected adverse reactions described in the scientific and medical literature are provided in VI.B.1.1.2. As regards the screening of the scientific and medical literature, the requirements provided in this Module are part of the wider literature searches which need to be conducted for PSUR/PBRERs (see Module VII).

MAHs should monitor all the active substances for which they hold a marketing authorization in the KSA by accessing a widely used systematic literature review and reference database, in line with the principles detailed in VI.B.1.1.2 and in VI Appendix 2.

Articles can be excluded from the reporting of ICSRs by the MAH if another company's branded medicinal product is the suspected medicinal product. In the absence of a specified medicinal product source and/or invented name, ownership of the medicinal product should be assumed for articles about an active substance, unless alternative reasons for exclusion detailed hereafter apply.

- Where ownership of the medicinal product by the MAH can be excluded on the basis of the criteria detailed in VI.C.2.1.;
- For ICSRs identified in the scientific and medical literature that originate in a country where a company holds a marketing authorization but has never commercialized the medicinal product;
- For literature articles, which present data analyses from publicly available databases or, which summarize results from post-authorization studies (See VI.C.1.2). This type of literature article describes adverse reactions, which occur in a group of patients with a designated medicinal product with the aim of identifying or quantifying a safety hazard related to a medicinal product, and aggregated data on patients are often presented in tables or line listings. The main objective of those studies is to detect/evaluate specific risks that could affect the overall benefit-risk balance of a medicinal product.

New and significant safety findings presented in these articles, for which reporting is not required, should however be discussed in the relevant sections of the concerned PSUR/PBRER (see Module VII) and analyzed as regards their overall impact on the medicinal product benefit-risk profile. In addition, any new safety information, which may impact on the benefit-risk profile of a medicinal product, should be notified immediately to the SFDA

in accordance with the recommendations provided in VI.C.2.1.6.

The electronic reporting recommendations regarding suspected adverse reactions reports published in the scientific and medical literature are provided in VI.C.6.2.3.2.

VI.C.2.1.4. Suspected adverse reactions related to quality defect or falsified medicinal products

When a report of suspected adverse reactions is associated with a suspected or confirmed falsified medicinal product or quality defect of a medicinal product, a valid ICSR should be reported. The seriousness of the ICSR is linked to the seriousness of the reported suspected adverse reactions in accordance with the definitions provided in VI.A.2.4. Electronic reporting recommendations provided in VI.C.6.2.3.5 should be followed. In addition, in order to protect public health, it may become necessary to implement urgent measures such as the recall of one or more defective batch(es) of a medicinal product from the market. Therefore, MAHs should have a system in place to ensure that reports of suspected adverse reactions related to falsified medicinal products or to quality defects of a medicinal products are investigated in a timely fashion and that confirmed quality defects are notified separately to the manufacturer and to the SFDA.

VI.C.2.1.5. Suspected transmission via a medicinal product of an infectious agent

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product should be considered as a serious adverse reaction and such cases should be reported within 15 days in accordance with the requirements outlined in VI.C.4. If no other criterion is applicable, the seriousness of this ICSR should be considered as important medical event (see VI.A.2.4). This also applies to vaccines.

In the case of medicinal products derived from human blood or human plasma, hemovigilance procedures may also apply. Therefore, the MAH should have a system in place to communicate suspected transmission via a medicinal product of an infectious agent to the manufacturer, the relevant blood establishment(s) and the SFDA.

Any organism, virus or infectious particle (e.g. prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

A transmission of an infectious agent may be suspected from clinical signs or symptoms, or

laboratory findings indicating an infection in a patient exposed to a medicinal product.
Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a medicinal product, but the occurrence of unknown agents should also always be considered.
In the context of evaluating a suspected transmission of an infectious agent via a medicinal product, care should be taken to discriminate, whenever possible, between the cause (e.g., injection/ administration) and the source (e.g., contamination) of the infection and the clinical conditions of the patient at the time of the infection (immuno-suppressed /vaccinee).
Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned medicinal product increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect for which the procedures detailed in VI.C.2.1.4 should be applied.

VI.C.2.1.6. Emerging safety issues

Events may occur, which do not fall within the definition of reportable valid ICSRs, and thus are not subject to the reporting requirements, even though they may lead to changes in the known benefit-risk balance of a medicinal product and/or impact on public health. Examples include:

- Major safety concerns identified in the course of a non-interventional post-authorization study or of a clinical trial;
- Signal of a possible teratogen effect or of significant hazard to public health;
- Safety issues published in the scientific and medical literature;
- Safety issues arising from the signal detection activity (see Module IX) or emerging from a new ICSR and which impact on the benefit-risk balance of the medicinal product and/or have implications for public health;
- Safety issues related to the use outside the terms of the marketing authorization;
- Safety issues due to misinformation in the product information;
- Marketing authorization withdrawal, non-renewal, revocation or suspension outside the KSA for safety-related reasons;
- Urgent safety restrictions outside the KSA;
- Safety issues in relation to the supply of raw material; or

These events/observations, which may affect the benefit-risk balance of a medicinal product, are not to be submitted as ICSRs. They should be notified as Emerging Safety Issues in writing to the SFDA where the medicinal product is authorized and to the SFDA via email (NPC.Drug@sfda.gov.sa); this should be done immediately when becoming aware of them and no longer than 7 calendar days. 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 PSUR/PBRER of the authorized medicinal product.

VI.C.2.1.7. Period between the submission of the marketing authorization application and the granting of the marketing authorization

In the period between the submission of the marketing authorization application and the granting of the marketing authorization, information (quality, non-clinical, clinical) that could impact on the benefit-risk balance of the medicinal product under evaluation may become available to the applicant. It is the responsibility of the applicant to ensure that this information is immediately submitted in accordance with the modalities described in VI.C.2.1.6 to the SFDA where the application is under assessment.

VI.C.2.1.8. Period after suspension, revocation or withdrawal of marketing authorization

The MAH shall continue to collect any reports of suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorization. The reporting requirements outlined in VI.C.4 remain.

Where a marketing authorization is withdrawn or revoked, the former MAH is encouraged to continue to collect spontaneous reports of suspected adverse reactions originating in the KSA to for example facilitate the review of delayed onset adverse reactions or of retrospectively notified cases.

VI.C.2.1.9. Period during a public health emergency

In the event of a public health emergency, regular reporting requirements may be amended. Such arrangements will be considered on a case-by-case basis and will be appropriately notified on the SFDA website.

VI.C.2.1.10. Reports from patient support programs and market research programs

A patient support program is an organized system where a MAH receives and collects information relating to the use of its medicinal products. Examples are post-authorization patient support and disease management programs, surveys of patients and healthcare providers, information gathering on patient compliance, or compensation/re-imbursement schemes.

A market research program refers to the systematic collection, recording and analysis by a MAH of data and findings about its medicinal products, relevant for marketing and business development.

Safety reports originating from those programs should be considered as solicited reports. MAHs should have the same mechanisms in place as for all other solicited reports (See VI.C.2.1.2) to manage that information and report valid cases of adverse reactions, which are suspected to be related to the concerned medicinal product.

Valid ICSRs should be reported as solicited in accordance with the electronic reporting requirements provided in VI.C.6.2.3.7.

VI.C.3. Reporting time frames of ICSRs

The general rules in relation to the reporting of initial and follow-up reports, including those for defining the clock start are detailed in VI.B.7.

Type of Report	Reporting Timeframe
Serious unexpected adverse event	Within 15 days
Non-serious unexpected adverse event	Within 15 days
Serious expected adverse event	Within 15 days
Non-serious expected adverse event	Within 90 days
Product Quality	Immediately (within 1 day)
Lack of Efficacy	Within 15 days

This should be done in accordance with the reporting modalities detailed in VI.C.4.

a. Serious ICSRs

- MAHs shall report all serious ICSRs that occur in the KSA.

- MAHs shall report to the NPC database all serious ICSRs that occur outside the KSA.

b. Non-Serious ICSRs

- MAHs shall report all non-serious ICSRs that occur in the KSA.

VI.C.4. Reporting modalities

VI.C.4.1 Interim arrangements

a. Serious ICSRs

- Marketing authorisation holders shall submit all serious ICSRs that occur inside or outside the KSA, including those received from international authorities, to the NPC database only.

b. Non-Serious ICSRs

- Marketing authorisation holders shall submit all non-serious ICSRs that occur in the KSA to the NPC database.

VI.C.5. Collaboration with the World Health Organization and the SFDA

The SFDA shall make available to the WHO Collaborating Centre for International Drug Monitoring all suspected adverse reaction reports occurring in the KSA.

VI.C.6. Electronic exchange of safety information in the KSA

VI.C.6.1. Applicable guidelines, definitions, international formats, standards and terminologies

For the classification, retrieval, presentation, risk-benefit evaluation and assessment, electronic exchange and communication of pharmacovigilance and medicinal product information, marketing authorisation holders and the SFDA shall adhere to the legal requirements.

In addition the following guidelines should be applied:

- The ICH guidelines detailed in VI.B.8;

- 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.

VI.C.6.2. Electronic Reporting of Individual Case Safety Reports

The reporting of valid ICSRs electronically, by marketing authorisation holders, is mandatory for all medicinal products authorised. Non-adherence to this requirement constitutes a non-compliance with KSA legislation.

VI.C.6.2.1. Preparation of Individual Case Safety Reports

VI.C.6.2.1.1. General principles

It is recognised that it is often difficult to obtain all the details on a specific case. However, the complete information (medical and administrative data) for a valid ICSR that is available to the sender should be reported in a structured manner in the relevant ICH-E2B(R2) data elements (which should be repeated as necessary when multiple information is available) and in the narrative section (see VI.C6.2.1.4). This applies to all types of ICSRs, such as reports with initial information on the case, follow-up information and cases highlighted for nullification.

VI.C.6.2.1.2. Information on suspect, interacting and concomitant medicinal products

For combination medicinal products, which contain more than one active substance, each active substance needs to be reflected individually in the data element ‘Active substance name(s)’ (ICH E2B(R2) B.4.k.2.2), which needs to be repeated for each active substance contained in the combination medicinal product.

When the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the active substance(s) of the medicinal product and where the proprietary medicinal product can be one of two or more possible generics, which have a different composition depending on the country where the medicinal product is marketed, the ICSR should be populated as follows:

- data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the proprietary/branded medicinal product name as reported by the primary source;

- data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with the active substance(s) that correspond(s) to the composition of the proprietary/branded medicinal product of the country where the reaction/event occurred.

However if the information is available on:

- the 'Identification of the country where the drug was obtained' (data element ICH E2B(R2) B.4.k.2.3),
- the 'Authorization/application number' (data element ICH-E2B(R2) B.4.k.4.1),
- the 'Country of authorization/application' (data element ICH-E2B(R2) B.4.k.4.2), and/or
- the 'Batch/lot number' (data element ICH-E2B(R2) B.4.k.3), the composition with regard the active substance(s) of the proprietary medicinal product should be provided accordingly.

Where the primary source reports a suspect or interacting branded/proprietary medicinal product name without indicating the pharmaceutical form/presentation of the product and where the proprietary/branded medicinal product can be one of two or more possible pharmaceutical forms/presentations, which have different compositions in a country, the ICSR should be populated as follows:

- data element 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) should be populated with the medicinal product name as reported by the primary source;
- data element 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) should be completed with those active substances which are in common to all pharmaceutical forms/presentations in the country of authorisation.

Where medicinal products cannot be described on the basis of the active substances or the invented names, for example when only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should only be reflected in the case narrative (data element ICH-E2B(R2) B.5.1). The data elements ‘Proprietary medicinal product name’ (ICH-E2B(R2) B.4.k.2.1) and ‘Active substance name(s)’ (ICH-E2B(R2) B.4.k.2.2) should not be populated. The

same applies if a suspected food interaction is reported (e.g. to grapefruit juice).

Where a case of adverse reactions is reported to be related only to a therapeutic class, it is considered incomplete and does not qualify for reporting (see VI.B.2). Efforts should be made to follow-up the case in order to collect the missing information regarding the suspected medicinal product (see VI.B.3).

As regards the reporting of drug interactions, which concerns drug/drug (including biological products), drug/food, drug/device, and drug/alcohol interactions, the coding of the interaction should be performed in Section 'Reactions/Events' (ICH-E2B(R2) B.2) in line with the latest version of the ICH-Endorsed Guide for MedDRA Users - MedDRA Term Selection: Points to Consider Document. In addition, for drug/drug interactions, information on the active substances/proprietary medicinal product names should be provided in the Section 'Drug information' (ICH-E2B(R2) B.4), which should be characterised as interacting in the data element 'Characterisation of drug role' (ICH-E2B(R2) B.4.k.1).

If the primary source suspects a possible causal role of one of the ingredients (e.g., excipient or adjuvant) of the suspected medicinal product, this information should be provided in the Section 'Drug information' (ICH-E2B(R2) B.4) as a separate entry in addition to the information given regarding the suspected medicinal product. This should also be specified in the case narrative (data element ICH-E2B(R2) B.5.1). If available, tests results (positive or negative) in relation to the causal role of the suspected ingredient should be included in the section 'Results of tests and procedures relevant to the investigation of the patient' (ICH E2B(R2) B.3).

VI.C.6.2.1.3. Suspected adverse reactions

All available information shall be provided for each individual case. The coding of diagnoses and provisional diagnoses with signs and symptoms in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1) should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider.

In practice, 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 in the ICH-E2B(R2)

section B.2 'Reaction(s)/event(s)'. If no diagnosis is provided, all reported signs and symptoms should be listed and MedDRA coded in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'. If these signs and symptoms are typically part of a diagnosis, the diagnosis can be MedDRA coded in addition by the SFDA or marketing authorisation holders in the ICH-E2B(R2) data element B.5.3 ‘Sender's diagnosis/syndrome and/or reclassification of reaction/event'.

If in the narrative other events have been reported, which are not typically signs or symptoms of the primary source's diagnosis or provisional diagnosis, and those events are suspected to be adverse reactions, they should also be listed and MedDRA coded in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'.

In case if the SFDA or a marketing authorisation holder disagrees with the diagnosis reported by the primary source, an alternative diagnosis can be provided in the ICH-E2B(R2) data element B.5.3 ‘Sender's diagnosis/syndrome and/or reclassification of reaction/event’ in addition to the reported diagnosis provided in the ICH-E2B(R2) section B.2 'Reaction(s)/event(s)'. In this situation, a reasoning should be included in the data element ‘Sender’s comments’ (ICH-E2B(R2) B.5.4) (See VI.C.6.2.2.4).

In the event of death of the patient, the date, cause of death including autopsy-determined causes shall be provided . If the death is unrelated to the reported suspected adverse reaction(s) and is linked for example to disease progression, the seriousness criterion of the ICSR should not be considered as fatal.

VI.C.6.2.1.4. Case narrative, causality assessment and comments

A case narrative (data element ICH-E2B(R2) B.5.1) shall be provided, where possible, for all cases with the exception of non-serious cases. 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. Any relevant autopsy or post-mortem findings shall also be summarised.

The narrative should be presented in line with the recommendations described in Chapter 5.2 of the ICH-E2D guideline. In this aspect, it should serve as a comprehensive, stand-alone “medical report” containing all known relevant clinical and related information, including patient characteristics, therapy details, medical history, clinical course of the event(s), diagnosis, adverse reactions and their outcomes, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes the suspected adverse

reactions. An example of a standard narrative template is available in the Report of the CIOMS Working Group V[40].

The information provided in the narrative should be consistent with the data appropriately reflected in all the other relevant ICH-E2B(R2) data elements of the ICSR.

Where available, comments from the primary source on the diagnosis, causality assessment or other relevant issue, should be provided in the data element 'Reporter's comments' (ICH-E2B(R2) B.5.2). The SFDA and marketing authorisation holders may provide an assessment of the case and describe a disagreement with, and/or alternatives to the diagnoses given by the primary source (See VI.C.6.2.1.3). This should be done in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4), where discrepancies or confusions in the information notified by the primary source may also be highlighted. Where applicable, a summary of the points of concerns and actions proposed should also be included in the data element 'Sender's comments' (ICH-E2B(R2) B.5.4), if the ICSR leads to notification of an Emerging Safety Issue (see VI.C.2.1.6). The degree of suspected relatedness of each medicinal product to the adverse reaction(s) may be indicated in the data element 'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18), which should be repeated as necessary. This also allows presenting the degree of relatedness from different sources or with different methods of assessment.

VI.C.6.2.1.5. Test results

Results of tests and procedures relevant to the investigation of the patient shall be provided.

As described in the ICH-E2B(R2) guideline, the section B.3 'Results of tests and procedures relevant to the investigation of the patient' should capture the tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate (exclude) a non-drug cause, (e.g., serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative results should be reported.

The coding of investigations should be performed in line with the latest version of the ICH-Endorsed Guide for MedDRA Users, MedDRA Term Selection: Points to Consider. If it is not possible to provide information on tests and test results in a structured manner, provisions have been made to allow for the transmission of the information as free text in the data element ICH-E2B(R2) B.3.2. 'Results of tests and procedures relevant to the investigation'.

VI.C.6.2.1.6. Supplementary information

Key information from supplementary records should be provided in the relevant section of the ICSR, and their availability should be mentioned in the data element 'List of documents held by sender' (ICH-E2B(R2) A.1.8.2). Other known case identifiers relevant for the detection of duplicates should be presented systematically in the data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11).

VI.C.6.2.1.7. Follow-up information

ICSRs are sent at different times to multiple receivers. Therefore the initial/follow-up status is dependent upon the receiver. For this reason an item to capture follow-up status is not included in the ICH-E2B(R2) data elements. However, the data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) taken together with the data element 'Sender identifier' (ICH E2B(R2) A.3.1.2) and the data element 'Sender's (case) report unique identifier' (ICH-E2B(R2) A.1.0.1) provide a mechanism for each receiver to identify whether the report being transmitted is an initial or a follow-up report. For this reason these items are considered critical for each transmission and a precise date should always be used (i.e. day, month, year). The data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) should therefore always be updated each time a follow-up information is received by the SFDA or a marketing authorisation holder, independently whether the follow-up information received is significant enough to be reported. The data element 'Date report was first received from the source' (ICH-E2B(R2) A.1.6) should remain unchanged to the date the SFDA or the marketing authorisation holder became aware of the initial report.

New information should be clearly identifiable in the case narrative (data element ICH-E2B(R2) B.5.1) and provided in a structured format in the applicable ICH-E2B(R2) data elements.

The SFDA or marketing authorisation holders should report follow-up information if significant new medical information has been received. Significant new information relates to for example new suspected adverse reaction(s), a change in the causality assessment and any new or updated information on the case that impacts on its medical interpretation.

Therefore, the identification of significant new information requiring to be reported always necessitates medical judgement.

Situations where the seriousness criteria and/or the causality assessment are downgraded (e.g. follow-up information leads to a change of the seriousness criteria from serious to non-serious; causality assessment is changed from related to non-related) should also be considered as significant changes and thus reported (See VI.B.7.1 for reporting time frames).

In addition, the SFDA or marketing authorisation holders should also report follow-up information, where new administrative information is available, that could impact on the case management; for example, if new case identifiers have become known to the sender, which may have been used in previous transmissions (data element 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11)). This information may be specifically relevant to manage potential duplicates. Another example refers to data element 'Additional available documents held by sender' (ICH-E2B(R2) A.1.8), whereby new documents that have become available to the sender may be relevant for the medical assessment of the case.

In contrast, a follow-up report which contains non-significant information does not require to be reported. This may refer, for example, to minor changes to some dates in the case with no implication for the evaluation or transmission of the case, or corrections of typographical errors in the previous case version. Medical judgement should be applied since a change to the birth date may constitute a significant modification (e.g. with implications on the age information of the patient). Similarly, a change of the status of a MedDRA code/term from current to non-current, due to a version change of MedDRA, can be considered as a non-significant change as long as this change has no impact on the medical content of a case. However, an amendment of the MedDRA coding due to a change in the interpretation of a previously reported suspected adverse reaction may constitute a significant change and therefore should be reported.

In situations where the case is modified without impacting on its medical evaluation, while no new follow-up is received (e.g., for correcting a mistake or typographical error), the date of receipt of the most recent information reported in the data element 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7) should not be changed. This data element should however be updated in any other situations, to the date when new follow-up information is received (independently whether it is significant or not) or to the date when changes are made which impact on the interpretation of the case.

Where follow-up information of a case initially reported by a marketing authorisation holder

is received directly by the SFDA, the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) of the initial report should be maintained, in adherence with the ICH-E2B(R2) rules.

VI.C.6.2.1.8. What to take into account for data privacy laws

To detect, assess, understand and prevent adverse reactions and to identify, and take actions to reduce the risks of, and increase the benefits from medicinal products for the purpose of safeguarding public health.

VI.C.6.2.1.9. Handling of languages

The ICH-E2B(R2) concept for the electronic reporting of ICSRs is based on the fact that structured and coded information is used for data outputs of pharmacovigilance systems (e.g. listings) and for signal detection. However, for scientific case assessment and signal evaluation, the medical summary provided in the data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1) is normally required (see VI.6.2.1.4).

Where suspected adverse reactions are reported in narrative and textual descriptions in English language, the original verbatim text and the summary thereof in English shall be provided by the marketing authorisation holder. For those reports, case translations shall be provided when requested by the SFDA for the evaluation of potential signals.

VI.C.6.2.1.10. Nullification of cases

In line with the ICH-E2B(R2) guideline, the nullification of individual cases 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. It is essential to use the same case report numbers previously submitted in the data element 'Sender's (case) safety report unique identifier' (ICH-E2B(R2) A.1.0.1) and in the data element 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10).

A nullified case is one that should no longer be considered for scientific evaluation. The process of the nullification of a case is by means of a notification by the sender to the receiver that this is no longer a valid case.

VI.C.6.2.2. Special situations

VI.C.6.2.2.1. Use of a medicinal product during pregnancy or breastfeeding

General recommendations are provided in VI.B.6.1.

With regard to the electronic reporting of parent-child/foetus cases, the following should be adhered to:

- In the situation where a foetus or nursing infant is exposed to one or several medicinal products through the parent and experiences one or more suspected adverse reactions (other than early spontaneous abortion/foetal demise), information on both the parent and the child/foetus should be provided in the same report. These cases are referred to as parent-child/foetus reports. The information provided in the section 'Patients characteristics' (ICH-E2B(R2) B.1) applies only to the child/foetus. The characteristics concerning the parent (mother or father), who was the source of exposure to the suspect medicinal product should be provided in the data element 'For a parent-child/fetus report, information concerning the parent' (ICH-E2B(R2) B.1.10). If both parents are the source of the suspect drug(s) then the case should reflect the mother's information in the data element 'For a parent-child/fetus report, information concerning the parent' (ICH E2B(R2) B.1.10). The data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1) should describe the entire case, including the father's information.
- If both the parent and the child/foetus experience suspected adverse reactions, two separate reports, i.e. one for the parent (mother or father) and one for the child/foetus, should be created but they should be linked by using the data element 'Identification number of the report which is linked to this report' (ICH-E2B(R2) A.1.12) in each report.
- If there has been no reaction affecting the child, the parent-child/foetus report does not apply; i.e. the section 'Patients characteristics' (ICH-E2B(R2) B.1) applies only to the parent (mother or father) who experienced the suspected adverse reaction.
- For those cases describing miscarriage or early spontaneous abortion, only a parent report is applicable, i.e. the section 'Patients characteristics' (ICH-E2B(R2) B.1) apply to the mother. However, if the suspect medicinal product was taken by the father, the data element 'Additional information on drug' (ICH-E2B(R2) B.4.k.19) should specify that the medication was taken by the father.

VI.C.6.2.2.2. Suspected adverse reaction reports published in the scientific and medical literature

SFDA requirements in relation to the monitoring of suspected drug reactions reported in the scientific and medical literature are provided in VI.C.2.1.3. With regard to the electronic

reporting of ICSRs published in the scientific and medical literature, the following applies:

- The literature references shall be included in the data element 'Literature reference(s)' (ICH-E2B(R2) A.2.2) in the Vancouver Convention (known as "Vancouver style").
- A comprehensive English summary of the article shall be provided in the data element 'Case narrative including clinical course, therapeutic measures, outcome and additional relevant information' (ICH-E2B(R2) B.5.1) [IR Art 28 (3) (b)].
- Upon request of the SFDA, for specific safety review, a full translation in English and a copy of the relevant literature article shall be provided by the marketing authorisation holder that transmitted the initial report, taking into account copyright restrictions.

VI.C.6.2.2.3. Suspected adverse reactions related to overdose, abuse, off-label use, misuse, medication error or occupational exposure

If a case of overdose, abuse, off-label use, misuse, medication error or occupational exposure is reported with clinical consequences, the MedDRA Lowest Level Term code, corresponding to the term closest to the description of the reported overdose, abuse, off-label use, misuse, medication error or occupational exposure should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).

VI.C.6.2.2.4. Lack of therapeutic efficacy

If the primary source suspects a lack of therapeutic efficacy, the MedDRA Lowest Level Term code, corresponding to the term closest to the description of the reported lack of therapeutic efficacy, should be provided in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).

Unless aggravation of the medical condition occurs, the indication for which the suspected medicinal product was administered should not be included in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term).

VI.C.6.2.2.5. Suspected adverse reactions related to quality defect or falsified medicinal products

SFDA requirements are provided in VI.C.2.1.4. In order to be able to clearly identify cases related to quality defect or falsified medicinal products when they are exchanged between

stakeholders, the following recommendations should be applied:

a. Quality defect

Where a report of suspected adverse reactions is associated with a suspected or confirmed quality defect of a medicinal product, the MedDRA Lowest Level Term code of the term corresponding most closely to the product quality issue, should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).

b. Falsified medicinal products

Where a report of suspected adverse reactions is associated with a suspected or confirmed falsified ingredient, active substance or medicinal product, the MedDRA Lowest Level Term code of the term corresponding most closely to the reported information should be added to the observed suspected adverse reaction(s) in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1). Information on the suspected medicinal product, active substance(s) or excipient(s) should be provided in the data elements 'Proprietary medicinal product name' (ICH-E2B(R2) B.4.k.2.1) and/or 'Active substance name(s)' (ICH-E2B(R2) B.4.k.2.2) as reported by the primary source.

VI.C.6.2.2.6. Suspected transmission via a medicinal product of an infectious agent

The coding of a suspected transmission of an infectious agent via a medicinal product in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1) should be performed.

In addition, if the infectious agent is specified, the MedDRA Lowest Level Term code corresponding to the infectious agent should also be included in the data element 'Reaction/event in MedDRA terminology (Lowest Level Term)' (ICH-E2B(R2) B.2.i.1).

VI.C.6.2.2.7. Reports originating from organised data collection systems and other systems

General safety reporting requirements in the KSA for post-authorisation studies are provided in VI.C.1 and VI.C.2.1.2. Individual case safety reports originating from those studies shall contain information on study type, study name and the sponsor's study number or study registration number [IR Art 28 (3)(c)]. This should be provided in ICH E2B(R2) section A.2.3 'Study identification'.

Safety reporting requirements regarding patient support programmes or market research

programmes are provided in VI.C.2.1.10.

The following reporting rules should be applied based on (i) the type of data collection system and (ii) whether the suspected medicinal product is part of the scope of the data collection system.

1. For cases of suspected adverse reactions (i) in relation to those adverse events for which the protocol of non-interventional post-authorisation studies does not provide differently and requires their systematic collection ii) originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is required or (iii) originating from patient support programmes, or market research programmes:

a) Where the adverse reaction is suspected to be related at least to the studied (or supplied) medicinal product:

- the report should be considered as solicited;
- the ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Report from study';
- the ICH E2B(R2) data element A.2.3.3 'Study type in which the reaction(s)/event(s) were observed' should be populated with the value ‘Other studies’ or 'Individual patient use'.

b) Where the adverse reaction is only suspected to be related to a medicinal product which is not subject to the scope of the organised data collection system and there is no interaction with the studied (or supplied) medicinal product:

- the report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;
- The ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.

2. For suspected adverse reactions (i) in relation to those adverse events for which the protocol of non-interventional post-authorisation studies provides differently and does not require their systematic collection (see VI.C.1.2.1.) or (ii) originating from compassionate use or named patient use conducted in Member States where the active collection of adverse events occurring in these programmes is not required (see VI.C.1.2.2.):

3. For clinical trial conducted and where the adverse reaction is only suspected to be related to a non-investigational medicinal product (or another medicinal product which is not subject

to the scope of the clinical trial) and there is no interaction with the investigational medicinal product:

The report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;

- The report should be considered as spontaneous report; as such it conveys the suspicion of the primary source;
- The ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.

VI.C.6.2.2.8. Receipt of missing minimum information

When missing minimum information has been obtained about a non-valid ICSR, the following rules should be applied:

• The data element ‘Date report was first received from source’ (ICH-E2B(R2) A.1.6) should contain the date of receipt of the initial non-valid ICSR;

• The data element ‘Date of receipt of the most recent information for this report’ (ICH-E2B(R2) A.1.7) should contain the date when all the four elements of the minimum information required for reporting have become available;

• Clarification should be provided in the case narrative (data element ICH-E2B(R2) B.5.1) that some of the four elements were missing in the initial report.;

• As for any reported cases, compliance monitoring is performed against the data element ‘Date of receipt of the most recent information for this report’ (ICH-E2B(R2) A.1.7).

VI.C.6.2.3. Data quality of individual case safety reports transmitted electronically and duplicate management

Specific quality system procedures and processes shall be in place in order to ensure;

- The submission of accurate and verifiable data on serious and non-serious suspected adverse reactions to the NPC database within the table specified in *(VI.C.3.)*.
- The quality, integrity and completeness of the information submitted on the risks of medicinal products, including processes to avoid duplicate submissions.

In this regard, marketing authorisation holders should have in place an audit system, which ensures the highest quality of the ICSRs transmitted electronically to the NPC database within the correct time frames, and which enables the detection and management of duplicate ICSRs

in their system. Those transmitted ICSRs should be complete, entire and undiminished in their structure, format and content.

A review of the ICSRs quality, integrity and compliance with the reporting time frames will be performed by the SFDA at regular intervals for all organisations reporting to the NPC database. Feedback from these reviews will be provided to those organisations.

VI.C.6.2.4. Electronic re-transmission of ICSRs between multiple senders and receivers

During this re-transmission process, information on the case should not in principle be omitted or changed if no new information on the case is available to the re-transmitting sender.

Exceptions apply to the following data elements or sections:

- 'Sender's (case) safety report unique identifier' (ICH-E2B(R2) A.1.0.1);
- 'Date of this transmission' (ICH-E2B(R2) A.1.3);
- 'Date report was first received from source' (ICH-E2B(R2) A.1.6), for initial reports;
- 'Date of receipt of the most recent information for this report' (ICH-E2B(R2) A.1.7);
- 'Information on sender and receiver of case safety report' (ICH-E2B(R2) A.3);
- 'Relatedness of drug to reaction(s)/event(s)' (ICH-E2B(R2) B.4.k.18);
- 'Sender's diagnosis/syndrome and/or reclassification of reaction/event' (ICH-E2B(R2) B.5.3);
- 'Sender's comments' (ICH-E2B(R2) B.5.4).

In the interest of improving data quality, in case of errors or inconsistencies in the report, the re-transmitters should go back to the originator of the report to correct the case accordingly. However, if this cannot be done within normal reporting time frame, the re-transmitter can correct information that has been incorrectly structured.

In addition, any electronic data interchange partner should adhere to the ICH-E2B(R2) rules regarding the provision of follow-up information, whereby the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) should be maintained in accordance with the ICH-E2B(R2) guideline. Non-adherence to these administrative requirements endangers the electronic case management and leads to the potential for unnecessary duplication of reports in the receiver's database.

VI.C.6.2.5. Electronic reporting through company's headquarters

If a pharmaceutical company decides to centralise the electronic reporting of ICSRs (e.g. by reporting through the company's global or a headquarter), the following should be taken into

account:

- the central reporting arrangement should be clearly specified in the marketing authorisation holder's pharmacovigilance system master file and in the internal standard operating procedures;
- the company's headquarter designated for reporting the ICSRs should be registered with NPC.

MODULE VII – PERIODIC BENEFIT RISK EVALAUTION REPORT/ PERIODICSAFETY UPDATE REPORT (PBRER/PSUR)

VII.A. INTRODUCTION

PSUR/PBRERs are pharmacovigilance documents intended to provide an evaluation of the benefit-risk balance of a medicinal product for submission by MAHs at defined time points during the post-authorization phase.

The format of PSUR/PBRERs shall follow the structure described in the annex 1. This Module provides guidance on the preparation, submission and assessment of PSUR/PBRERs.

The scope, objectives, format and content of the PSUR/PBRER are described in VII.B.. The required format and content of PSUR/PBRERs in the KSA are based on those for the Periodic Benefit Risk Evaluation Report (PBRER) described in the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)). The PBRER replaces the PSUR/PBRER format previously described in the ICH-E2C(R1). In the KSA, the report shall be described and named as PSUR/PBRER.

Further details and guidance for the submission of PSUR/PBRERs in the KSA, including the frequency of submission are provided in VII.C.

MAHs should submit PSUR/PBRERs to the SFDA according to the following timelines:

- within 70 calendar days of the data lock point for PSUR/PBRERs covering intervals up to 12 months (including intervals of exactly 12 months); and
- within 90 calendar days of the data lock point for PSUR/PBRERs covering intervals in excess of 12 months;
- the timeline for the submission of ad hoc PSUR/PBRERs requested by the SFDA will normally be specified in the request, otherwise the ad hoc PSUR/PBRERs should be submitted within 90 calendar days of the data lock point.

It should be noted that detailed listings of individual cases shall not be included systematically. The PSUR/PBRER should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation.

The obligations imposed in respect of PSUR/PBRERs should be proportionate to the risks posed by medicinal products. PSUR/PBRER reporting should therefore be linked to the RMPs

(RMPs) of a medicinal product (see Module V). The "modular approach" of the PSUR/PBRER described in VII.B.5. aims to minimize duplication and improve efficiency during the preparation and review of PSUR/PBRERs along with other regulatory documents such as the development safety update report (DSUR) or the safety specification in the RMP, by enabling the common content of particular sections where appropriate to be utilized interchangeably across different PSUR/PBRERs, DSURs and RMPs.

The new legislation also waives the obligation to submit PSUR/PBRERs routinely for generic medicinal products, well-established use medicinal products, homeopathic medicinal products and traditional herbal medicinal products. For such products, PSUR/PBRERs shall be submitted where there is a condition in the marketing authorization or when requested by the SFDA on the basis of concerns relating to pharmacovigilance data or due to the lack of PSUR/PBRERs for an active substance after its authorization. However, if the generic product is the first registered in Saudi Arabia, the MAH should submit the PSUR/PBRER to SFDA according to timelines provided in VII.C.

SFDA shall assess PSUR/PBRERs to determine whether there are new risks or whether risks have changed or whether there are changes to the benefit-risk balance of medicinal products. As part of the assessment, it should be considered whether further investigations need to be carried out and whether any action concerning the marketing authorizations of products containing the same active substance or the same combination of active substances, and their product information is necessary.

This GVP Module VII may be reviewed and updated following further development and finalization of the ICH-E2C(R2) guideline on PBRER.

VII.B. STRUCTURES AND PROCESSES

VII.B.1. Objectives of the periodic safety update report

The main objective of a PSUR/PBRER is to present a comprehensive and critical analysis of the benefit-risk balance of the medicinal product considering new or emerging information in the context of cumulative information on risks and benefits. The PSUR/PBRER is therefore a tool for post-authorization evaluation at defined time points in the lifecycle of a product.

For the purposes of lifecycle benefit-risk management, it is necessary to continue evaluating the risks and benefits of a medicine in everyday medical practice and long-term use in the

post-authorization phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorization clinical trials. A different benefit-risk profile may emerge as pharmacovigilance reveals further information about safety. The MAH should therefore re-evaluate the benefit-risk balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance and risk management (see Module V) to facilitate optimization of the benefit-risk balance through effective risk minimization.

A PSUR/PBRER should not be used to provide initial notification of significant new safety information or, as a general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted (see Module IX and XII).

VII.B.2. Principles for the evaluation of the benefit-risk balance within PSUR/PBRERs and scope of the information to be included

Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimization.

After a marketing authorization is granted, it is necessary to continue evaluating the benefits and risks of medicinal products in actual use and/or long-term use, to confirm that the benefit-risk profile remains favorable.

The analysis of the benefit-risk balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available, with reasonable and appropriate effort, during the reporting interval for the medicinal product in the context of what was known previously.

The risk evaluation should be based on all uses of the medicinal product. The scope includes evaluation of safety in real medical practice including use in unauthorized indications and use which is not in line with the product information. If use of the medicinal product is identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PSUR/PBRER (e.g. use in pediatric population or in pregnant women). Sources of information on use outside authorization may include drug utilization data, information from spontaneous reports and publications in the literature.

The scope of the benefit information should include both clinical trial and real-world data in

authorized indications. The integrated benefit-risk evaluation should be based on all authorized indications but should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorized indications).

The evaluation should involve:

1. Critically examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risks.
2. Critically summarizing relevant new safety, efficacy and effectiveness information that could have an impact on the benefit-risk balance of the medicinal product.
3. Conducting an integrated benefit-risk analysis for all authorized indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorization for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the MAH does not have access to data from the clinical development period, the earliest possible applicable date should be used as starting point for the inclusion and evaluation of the cumulative information.
4. Summarizing any risk minimization actions that may have been taken or implemented during the reporting interval, as well as risk minimization actions that are planned to be implemented.
5. Outlining plans for signal or risk evaluations including timelines and/or proposals for additional pharmacovigilance activities.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the MAH shall draw conclusions in the PSUR/PBRER as to the need for changes and/or actions, including implications for the approved SPC for the product(s) for which the PSUR/PBRER is submitted.

VII.B.3. Principles for the preparation of PSUR/PBRERs

Unless otherwise specified by the SFDA, the MAH shall prepare a single PSUR/PBRER for all its medicinal products containing the same active substance with information covering all the authorized indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorized under different names and through separate procedures.

Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, shall be presented in a separate section of the PSUR/PBRER and any safety concerns shall be addressed accordingly. There might be exceptional scenarios where the preparation of separate PSUR/PBRERs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement should be obtained from the SFDA preferably at the time of authorization.

Case narratives shall be provided in the relevant risk evaluation section of the PSUR/PBRER where integral to the scientific analysis of a signal or safety concern. In this context, the term "case narratives" refers to clinical evaluations of individual cases rather than the CIOMS narratives. It should not be necessary to provide the actual CIOMS narrative text included in the ICSR but rather a clinical evaluation of important or illustrative cases in the context of the evaluation of the safety concern/signal.

The format and table of contents of all PSUR/PBRERs should include interval as well as cumulative data. As the PSUR/PBRER should be a stand–alone document based on cumulative data, summary bridging reports and addendum reports, introduced in ICH-E2C(R1) guideline, will not be accepted.

VII.B.4. Reference information

Risk minimization activities evaluated in the PSUR/PBRER include updates to the product information.

The reference product information for the PSUR/PBRER should include "core safety" and "authorized indications" components. In order to facilitate the assessment of benefit and benefit-risk balance by indication in the evaluation sections of the PSUR/PBRER, the reference product information document should list all authorized indications in ICH countries or regions. When the PSUR/PBRER is also submitted to other countries in which there are additional locally authorized indications, these indications may be either added to the reference product information or handled as a regional appendix as considered most appropriate by the MAH. The basis for the benefit evaluation should be the baseline important efficacy and effectiveness information summarized in the PSUR/PBRER section 17.1 ("Important baseline efficacy and effectiveness information").

Information related to a specific indication, formulation or route of administration should be

clearly identified in the reference product information.

The following possible options can be considered by the MAHs when selecting the most appropriate reference product information for a PSUR/PBRER:

- Company core data sheet (CCDS)

  − It is common practice for MAHs to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PSUR/PBRER is for each MAH to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR/PBRER as well as the main authorized indications for which benefit is evaluated.

    - When the CCDS does not contain information on authorized indications, the MAH should clearly specify which document is used as reference information for the authorized indications in the PSUR/PBRER.

- Other options for the reference product information

  − When no CCDS or CCSI exist for a product (e.g. where the product is authorized in only one country or region, or for established/generics products on the market for many years), the MAH should clearly specify the reference information being used. This may comprise national or regional product information such as the SPC.

    - Where the reference information for the authorized indications is a separate document to the reference safety information (the core safety information contained within the reference product information), the version in effect at the end of the reporting interval should be included as an appendix to the PSUR/PBRER (see VII.B.5.20.).

The MAH should continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PSUR/PBRER section 4 (“Changes to the reference safety information”) and where relevant, discussed in PSUR/PBRER section 16 (“Signal and risk evaluation”). These changes may include:

- Changes to contraindications, warnings/precautions sections;

- Addition to adverse reactions and interactions;
- Addition of important new information on use in overdose; and
- Removal of an indication or other restrictions for safety or lack of efficacy reasons.

The MAH should provide a clean copy of all versions of the reference product information in effect at the end of the reporting interval (e.g. different formulations included in the same PSUR/PBRER) as an appendix to the PSUR/PBRER (see VII.B.5.20.). The reference product information should be dated, and version controlled.

Where new information on safety that could warrant changes to the authorized product information (e.g. new ADR, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PSUR/PBRER, this information should be included in the PSUR/PBRER section 14 ("Late-breaking information"), if feasible.

If stipulated by applicable regional requirements, the MAH should provide, in the regional appendix, information on any final, ongoing and proposed changes to the national or local authorized product information.

VII.B.5. Format and contents of the PSUR/PBRER

The PSUR/PBRER shall be based on all available data and shall focus on new information which has emerged since the data lock point of the last PSUR/PBRER. Cumulative information should be considered when performing the overall safety evaluation and integrated benefit-risk assessment.

Because clinical development of a medicinal product frequently continues following marketing authorization, relevant information from post-authorization studies or clinical trials in unauthorized indications or populations should also be included in the PSUR/PBRER. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk evaluation where relevant and appropriate.

The PSUR/PBRER shall provide summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of their potential impact on the marketing authorization.

Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSUR/PBRERs include the following:

- Non-clinical studies;
- Spontaneous reports;
- Active surveillance systems (e.g. sentinel sites);
- Investigations of product quality;
- Product usage data and drug utilization information;
- Clinical trials, including research in unauthorized indications or populations;
- Observational studies, including registries;
- Patient support programs;
- Systematic reviews and meta-analysis;
- MAHs sponsored websites;
- Published scientific literature or abstracts, including information presented at scientific meetings;
- Unpublished manuscripts made available to the MAH;
- Licensing partners, other sponsors or academic institutions and research networks;
- Competent authorities (worldwide).

The above list is not intended to be all inclusive, and additional data sources may be used by the MAH to present safety, efficacy and effectiveness information in the PSUR/PBRER and to evaluate the benefit-risk balance, as appropriate to the product and its known and emerging important benefits and risks. When desired by the MAH, a list of the sources of information used to prepare the PSUR/PBRER can be provided as an appendix to the PSUR/PBRER.

For the purposes of this Module, sources of information include data regarding the active substance(s) included in the medicinal product, or the medicinal product that the MAH may reasonably be expected to have access to and that are relevant to the evaluation of the safety, and/or benefit-risk profile. It is therefore recognized that while the same format shall be followed for all products, the extent of the information provided may vary where justified according to what is accessible to the MAH. For example, for a MAH sponsored clinical trial, there should be access to patient level data while for a clinical trial not sponsored by the MAH, only the published report may be accessible.

When preparing the PSUR/PBRER, the ICH-E2C(R2) guideline (see Annex IV ICH-E2C(R2)) on PBRER should also be applied. Guidance on the titles, order and content of the PSUR/PBRER sections is provided in VII.B.5.1. to VII.B.5.20. When no relevant information is available for any of the sections, this should be stated.

Part I: Title page including signature

Part II: Executive Summary

Part III: Table of Contents

1. Introduction
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3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
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16. Signal and risk evaluation
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    18.2. Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices to the PSUR/PBRER

PSUR/PBRER title page

The title page should include the name of the medicinal product(s) and substance, international birth date, reporting interval, date of the report, MAH details and statement of confidentiality of the information included in the PSUR/PBRER.

The title page shall also contain the signature.

PSUR/PBRER executive summary

An executive summary should be placed immediately after the title page and before the table of contents. The purpose of the executive summary is to provide a concise summary of the content and the most important information in the PSUR/PBRER and should contain the following information:

- Introduction and reporting interval;
- Medicinal product(s), therapeutic class(es), mechanism(s) of action, indication(s), pharmaceutical formulation(s), dose(s) and route(s) of administration;
- Estimated cumulative clinical trials exposure;

- Estimated interval and cumulative exposure from marketing experience;
- Number of countries in which the medicinal product is authorized;
- Summary of the overall benefit-risk analysis evaluation (based on sub-section 18.2 “benefit-risk analysis evaluation” of the PSUR/PBRER);
- Actions taken and proposed for safety reasons including significant changes to the investigator brochure and post-authorization product information or other risk minimization activities;
- Conclusions.

PSUR/PBRER table of contents

The executive summary should be followed by the table of contents.

VII.B.5.1. PSUR/PBRER section “Introduction”

The MAH should briefly introduce the product(s) so that the PSUR/PBRER “stands alone” but it is also placed in perspective relative to previous PSUR/PBRERs and circumstances. The introduction should contain the following information:

- International birth date (IBD), the date of the first marketing authorization for any product containing the active substance granted to any company in any country in the world, and reporting interval.
- Medicinal product(s), therapeutic class(es), mechanism(s) of action, authorized indication(s), pharmaceutical form(s), dose(s) and route(s) of administration;
- A brief description of the population(s) being treated and studied;

VII.B.5.2. PSUR/PBRER section “Worldwide marketing authorization status"

This section of the PSUR/PBRER provides cumulative information and should contain a brief narrative overview including: date of the first authorization worldwide, indications(s), authorized dose(s), and where authorized.

VII.B.5.3. PSUR/PBRER section “Actions taken in the reporting interval for safety reasons”

This section of the PSUR/PBRER should include a description of significant actions related

to safety that have been taken worldwide during the reporting interval, related to either investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:

- A significant influence on the benefit-risk balance of the authorized medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development program.

If known, the reason for each action 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.

Examples of significant actions taken for safety reasons include:

Actions related to investigational uses:

1. Refusal to authorize a clinical trial for ethical or safety reasons;
2. Partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
3. Recall of investigational drug or comparator;
4. Failure to obtain marketing authorization for a tested indication including voluntary withdrawal of a marketing authorization application;
5. Risk management activities, including:

   – protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);

   - Restrictions in study population or indications;
   - Changes to the informed consent document relating to safety concerns;
   - Formulation changes;
   - Addition by regulators of a special safety-related reporting requirement;
   - Issuance of a communication to investigators or healthcare professionals; and
   - Plans for new studies to address safety concerns.

“Partial suspension” might include several actions (e.g. suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in

another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses). ICH-E2C(R2) guideline (see Annex IV).

Actions related to marketing experience:

- Failure to obtain or apply for a marketing authorization renewal;
- Withdrawal or suspension of a marketing authorization;
- Actions taken due to product defects and quality issues;
- Suspension of supply by the marketing authorization holder;
- Risk management activities including:
  - Significant restrictions on distribution or introduction of other risk minimization measures;
  - Significant safety-related changes in labelling documents including restrictions on use or population treated;
  - Communications to healthcare professionals; and
  - New post-marketing study requirement(s) imposed by competent authorities.

VII.B.5.4. PSUR/PBRER section "Changes to reference safety information"

This PSUR/PBRER section should list any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious ADRs, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR/PBRER.

VII.B.5.5. PSUR/PBRER section "Estimated exposure and use patterns"

PSUR/PBRERs shall provide an accurate estimate of the population exposed to the medicinal product, including all data relating to the volume of sales and volume of prescriptions. This estimate of exposure shall be accompanied by a qualitative and quantitative analysis of actual use, which shall indicate, where appropriate, how actual use differs from the indicated use based on all data available to the MAH, including the results of observational or drug utilization studies.

This PSUR/PBRER section should provide estimates of the size and nature of the population exposed to the medicinal product including a brief description of the method(s) used to

estimate the subject/patient exposure and the limitations of that method.

Consistent methods for calculating subject/patient exposure should be used across PSUR/PBRERs for the same medicinal product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR/PBRER introducing the change and any important difference between the results using the two methods should be highlighted.

VII.B.5.5.1. PSUR/PBRER sub-section "Cumulative subject exposure in clinical trials"

This section of the PSUR/PBRER should contain the following information on the patients studied in clinical trials sponsored by the MAH, if applicable presented in tabular formats:

- 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;
- more detailed cumulative subject exposure in clinical trials should be presented if available (e.g. sub-grouped by age, sex, and racial group for the entire development program); it is recognized that for old products, detailed data might not available;
- important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered;
- if clinical trials have been or are being performed in special populations (e.g. pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided as appropriate;
- when there are substantial differences in time of exposure between subjects randomized to the investigational medicinal product or comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years);
- investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate;
- if the serious adverse events from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available;
- for individual trials of particular importance, demographic characteristics should be provided separately.

Examples of tabular format for the estimated exposure in clinical trials are presented in VII. Appendix 1, tables VII.2, VII.3 and VII.4.

VII.B.5.5.2. PSUR/PBRER sub-section "Cumulative and interval patient exposure from marketing experience"

When possible, separate estimates should be provided for cumulative exposure (since the IBD) and interval exposure (since the data lock point of the previous PSUR/PBRER). Although it is recognized that it is often difficult to obtain and validate exposure data, the number of patients exposed should be provided whenever possible, along with the method(s) used to determine the estimate. Justification should be provided if it is not possible to estimate the number of patients exposed. In this case, alternative estimates of exposure, if available, should be presented along with the method(s) used to derive them. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to arrive at patient exposure estimates.

The data should be presented according to the following categories:

1. **Post-authorization (non-clinical trial) exposure:**

An overall estimation of patient exposure should be provided. In addition, the data should be presented by sex, age, indication, dose, formulation and region, where available. Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment.

When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

2. **Post-authorization use in special populations:**

Where post-authorization use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data would include non-interventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:

- pediatric population;
- elderly population;
- pregnant or lactating women;
- patients with hepatic and/or renal impairment;
- patients with other relevant co-morbidity;
- patients with disease severity different from that studied in clinical trials;
- sub-populations carrying relevant genetic polymorphism(s);
- populations with specific racial and/or ethnic origins.

3. Other post-authorization use:

If the MAH becomes aware of a pattern of use of the medicinal product, considered relevant for the interpretation of safety data, provide a brief description thereof. Such patterns may include, in particular, off-label use (e.g., an anti-epileptic drug used off-label for neuropathic pain and/or prophylaxis of migraine headaches). If known, the MAH may briefly comment on whether such use is supported by clinical guidelines, clinical trial evidence, or an absence of authorized alternative treatments. If quantitative use information is available, it should be provided.

Examples of tabular format for the estimated exposure from marketing experience are presented in VII. Appendix 1, tables VII.5 and VII.6.

VII.B.5.6. PSUR/PBRER section "Data in summary tabulations"

The objective of this PSUR/PBRER section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide)) and serious reactions from non-interventional studies and other non-interventional solicited source. At the discretion of the MAH graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) 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. When serious and non-serious events/reactions are included in the same ICSR, the individual seriousness per reaction should be reflected in the summary tabulations. Seriousness should not be changed specifically for the preparation of the PSUR/PBRERs.

VII.B.5.6.1. PSUR/PBRER sub-section "Reference information"

This sub-section of the PSUR/PBRER should specify the version(s) of the coding dictionary used for presentation of adverse events/reactions.

VII.B.5.6.2. PSUR/PBRER sub-section "Cumulative summary tabulations of serious adverse events from clinical trials"

This PSUR/PBRER sub-section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the MAH's clinical trials, from the DIBD to the data lock point of the current PSUR/PBRER. The MAH should explain any omission of data (e.g. clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organized by MedDRA SOC (listed in the internationally agreed order), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development program. Data can be integrated across the program. Alternatively, when useful and feasible, data can be presented by trial, indication, route of administration or other variables.

This sub-section should not serve to provide analyses or conclusions based on the serious adverse events.

The following points should be considered:

- Causality assessment is generally useful for the evaluation of individual rare ADRs. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all serious adverse events and not just serious adverse reactions for the investigational drug, comparators and placebo. It may be useful to give rates by dose.

- In general, the tabulation(s) of serious adverse events from clinical trials should include only those terms that were used in defining the case as serious and non-serious events should be included in the study reports.
- The tabulations should include blinded and unblinded clinical trial data. Unblinded serious adverse events might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g. expedited reporting), if applicable. Sponsors of clinical trials and MAHs should not unblind data for the specific purpose of preparing the PSUR/PBRER.
- Certain adverse events can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g. deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

An example of summary tabulation of serious adverse events from clinical trials can be found in VII. Appendix 1 table VII.7.

VII.B.5.6.3. PSUR/PBRER sub-section "Cumulative and interval summary tabulations from post-marketing data sources"

This sub-section of the PSUR/PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the data lock point of the current PSUR/PBRER. These adverse reactions are derived from spontaneous ICSRs including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide) and from solicited non-interventional ICSRs including those from non-interventional studies. Serious and non-serious reactions from spontaneous sources, as well as serious adverse reactions from non-interventional studies and other non-interventional solicited sources should be presented in a single table, with interval and cumulative data presented side-by-side. The table should be organized by MedDRA SOC (listed in the internationally agreed order). For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or

other variables.

As described in ICH-E2D guideline, for marketed medicinal products, spontaneously reported adverse events usually imply at least a suspicion of causality by the reporter.

Analysis or conclusions based on the summary tabulations should not be provided in this PSUR/PBRER sub-section.

An example of summary tabulations of ADRs from post-marketing data sources can be found in VII. Appendix 1 table VII.8.

VII.B.5.7. PSUR/PBRER section "Summaries of significant findings from clinical trials during the reporting interval"

This PSUR/PBRER section should provide a summary of the clinically important efficacy and safety findings during the reporting interval obtained from the sources specified in the sub-sections listed below. When possible and relevant, data categorized by sex and age (particularly pediatrics versus adults), indication, dose, and region should be presented.

In addition, the MAH should include an appendix listing the sponsored interventional trials with the primary aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval.

Signals arising from clinical trial sources should be tabulated in PSUR/PBRER Section 15 ("Overview on signals: new, ongoing or closed"). Evaluation of the signals, whether or not categorized as refuted signals or either potential or identified risk, that were closed during the reporting interval should be presented in PSUR/PBRER section 16.2 ("Signal evaluation"). New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterized in PSUR/PBRER sections 16.3 ("Evaluation of risks and new information") and 16.4 ("Characterization of risks") respectively.

VII.B.5.7.1. PSUR/PBRER sub-section "Completed clinical trials"

This sub-section of the PSUR/PBRER should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis. It could include information that supports or refutes previously identified safety concerns as

well as evidence of new safety signals.

VII.B.5.7.2. PSUR/PBRER sub-section "Ongoing clinical trials"

If the MAH is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this sub-section should briefly summarize the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

VII.B.5.7.3. PSUR/PBRER sub-section "Long term follow-up"

Where applicable, this sub-section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products).

VII.B.5.7.4. PSUR/PBRER sub-section "Other therapeutic use of medicinal product"

This sub-section of the PSUR/PBRER should include clinically important safety information from other programs conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH-E2D (e.g. expanded access programs, compassionate use programs, particular patient use, and other organized data collection).

VII.B.5.7.5. PSUR/PBRER sub-section "New safety data related to fixed combination therapies"

Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:

- If the active substance that is the subject of the PSUR/PBRERs is also authorized or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarize important safety findings from use of the combination therapy.
- If the product itself is a fixed combination product, this PSUR/PBRER sub-section should summarize important safety information arising from the individual components whether authorized or under development.

The information specific to the combination can be incorporated into a separate section(s) of

the PSUR/PBRER for one or all of the individual components of the combination.

VII.B.5.8. PSUR/PBRER section "Findings from non-interventional studies"

This section should also summarize relevant safety information or information with potential impact in the benefit-risk assessment from MAH-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programs). This should include relevant information from drug utilization studies when relevant to multiple regions.

The MAH should include an appendix listing MAH-sponsored non-interventional studies conducted with the primary 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 which were completed or ongoing during the reporting interval.

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the PSUR/PBRER (see VII.B.5.20. and VII.C.5.5.).

Summary information based on aggregate evaluation of data generated from patient support programs may be included in this section when not presented elsewhere in the PSUR/PBRER. As for other information sources, the MAH should present signals or risks identified from such information in the relevant sections of the PSUR/PBRER.

VII.B.5.9. PSUR/PBRER section "Information for other clinical trials and Sources"

VII.B.5.9 1. PSUR/PBRER sub-section "Other clinical trials"

This PSUR/PBRER sub-section should summarize information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources which are accessible by the MAH during the reporting interval (e.g. results from pool analysis or meta-analysis of randomized clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

VII.B.5.9 2. PSUR/PBRER sub-section "Medication errors"

This sub-section should summarize relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential

medication error is the recognition of circumstances that could lead to a medication error and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process and may involve patients, consumers, or healthcare professionals.

VII.B.5.10. PSUR/PBRER section "Non-clinical data"

This PSUR/PBRER section should summarize major safety findings from non-clinical in vivo and in vitro studies (e.g. carcinogenicity, reproduction or immunotoxicity studies) ongoing or completed during the reporting interval. Implications of these findings should be discussed in the section 16 ("Signal and risk evaluation") and section 18 ("Integrated benefit-risk analysis for authorized indications") of the PSUR/PBRER.

VII.B.5.11. PSUR/PBRER section "Literature"

This PSUR/PBRER section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the MAH became aware of during the reporting interval, when relevant to the medicinal product.

Literature searches for PSUR/PBRERs should be wider than those for individual adverse reaction cases as they should also include studies reporting safety outcomes in groups of subjects and other products containing the same active substance.

The special types of safety information that should be included, but which may not be found by a search constructed specifically to identify individual cases, include:

- pregnancy outcomes (including termination) with no adverse outcomes;
- use in pediatric populations;
- compassionate supply, named patient use;
- lack of efficacy;
- asymptomatic overdose, abuse or misuse;
- medication error where no adverse events occurred;
- important non-clinical safety results.

If relevant and applicable, information on other active substances of the same class should be

considered.

The publication reference should be provided in the style of the Vancouver Convention.

VII.B.5.12. PSUR/PBRER section "Other periodic reports"

This PSUR/PBRER section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSUR/PBRERs are prepared in agreement with the competent authority. In general, the MAH should prepare a single PSUR/PBRER for a single active substance (unless otherwise specified by the SFDA); however, if multiple PSUR/PBRERs are prepared for a single medicinal product, this section should also summarize significant findings from other PSUR/PBRERs if they are not presented elsewhere within the report.

When available, based on the contractual agreements, the MAH should summarize significant findings from periodic reports provided during the reporting interval by other parties (e.g. sponsors or other contractual partners).

VII.B.5.13. PSUR/PBRER section "Lack of efficacy in controlled clinical trials"

This section should summarize data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g. excess cardiovascular adverse events in a trial of a new anti-platelet medicine for acute coronary syndromes) that could reflect a significant risk to the treated population.

VII.B.5.14. PSUR/PBRER section "Late-breaking information"

The MAH should summarize in this PSUR/PBRER section the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR/PBRER. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the MAH, a data monitoring committee, or a competent authority (worldwide) has taken for safety reasons. New individual case reports should not be routinely included unless they are considered to constitute an important index case (i.e. the first instance of an important event) or an important safety signal or where they may add information to the evaluation of safety concerns already presented in the PSUR/PBRER (e.g. a well-documented case of aplastic

anemia in a medicinal product known to be associated with adverse effects on the bone marrow in the absence of possible alternative causes).

Any significant change proposed to the reference product information (e.g. new adverse reaction, warning or contraindication) which has occurred during this period, should also be included in this section of the PSUR/PBRER (see VII.B.4.), where feasible.

The data presented in this section should also be considered in the evaluation of risks and new information (see VII.B.5.16.3.).

VII.B.5.15. PSUR/PBRER section "Overview of signals: new, ongoing, or closed"

The general location for presentation of information on signals and risks within the PSUR/PBRER is shown in figure VII.1 (see VII.B.5.21.). The purpose of this section is to provide a high-level overview of signals that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation (including SFDA requests of safety signal evaluation reports that were closed or undergoing evaluation by MAH) at the end of the reporting interval. For the purposes of the PSUR/PBRER, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the MAH. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific medicine/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal ICSR, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide) (see Module IX).

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation, involve medical judgement and scientific interpretation of available data, which is presented in section 16 ("Signal and risk evaluation") of the PSUR/PBRER.

A new signal refers to a signal that has been identified during the reporting interval. Where new clinically significant information on a previously closed signal becomes available during the reporting interval of the PSUR/PBRER, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognized risk warrants further action to verify. New signals may be classified as closed or ongoing, depending on the status of

signal evaluation at the end of the reporting interval of the PSUR/PBRER.

Examples of new signals would therefore include new information on a previously:

- Close and refuted signal, which would result in the signal being re-opened.
- Identified risk where the new information suggests a clinically significant difference in the severity or frequency of the risk (e.g. transient liver enzyme increases are identified risks and new information indicative of a more severe outcome such as hepatic failure is received, or neutropenia is an identified risk and a well-documented case report of agranulocytosis with no presence of possible alternative causes is received).
- Identified risk for which a higher frequency or severity of the risk is newly found (e.g. in an indicated subpopulation).
- Potential risk which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimization activities.

Within this section, or as an appendix the 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 MAH became aware of the signal;
- status of the signal at the end of the reporting interval (close or ongoing);
- date when the signal was closed, if applicable;
- source of the signal;
- a brief summary of the key data;
- plans for further evaluation; and
- actions taken or planned.

An example of tabulation of signals can be found in VII. Appendix 2.

The detailed signal assessments for closed signals are not to be included in this section but instead should be presented in sub-section 16.2 (“Signal evaluation”) of the PSUR/PBRER.

Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a new signal should be provided in PSUR/PBRER sub-section 16.3 (“Evaluation of risks and new information”).

When a competent authority (worldwide) has requested that a specific topic (not considered

a signal) be monitored and reported in a PSUR/PBRER, the MAH should summarize the result of the analysis in this section if it is negative. If the specific topic becomes a signal, it should be included in the signal tabulation and discussed in sub-section 16.2 (“Signal evaluation”).

VII.B.5.16. PSUR/PBRER section “Signal and risk evaluation”

The purpose of this section of the PSUR/PBRER is to provide:

- A succinct summary of what is known about important identified and potential risks and missing information at the beginning of the reporting interval covered by the report (VII.B.5.16.1.).
- An evaluation of all signals closed during the reporting interval (VII.B.5.16.2.).
- An evaluation of new information with respect to previously recognised identified and potential risks (VII.B.5.16.3).
- An updated characterisation of important potential and identified risks, where applicable (VII.B.5.16.4.).
- A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (VII.B.5.16.5.).

A flowchart illustrating the mapping of signals and risks to specific sections/sub-sections of the PSUR/PBRER can be found in VII.B.5.21.

These evaluation sub-sections should not unnecessarily duplicate information presented in previous sections of the PSUR/PBRER but should rather provide interpretation and critical appraisal of the information, with a view towards characterizing the profile of those risks assessed as important or prompting regulatory action (e.g. labelling changes). In addition, as a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PSUR/PBRER but where integral to the scientific analysis of a signal or risk, a clinical evaluation of important or illustrative cases should be provided (see VII.B.3).

VII.B.5.16.1. PSUR/PBRER sub-section “Summary of safety concerns”

The purpose of this sub-section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. For products with an existing safety specification, this section is likely to be the same as the safety specification summary that is current at the start of the reporting interval of the PSUR/PBRER. It should provide the following safety information:

- important identified risks;
- important potential risks; and
- missing information.

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;
- potential impact on public health (frequency; size of treated population); and
- public perception of risk where it may impact public heath, (e.g., avoidance of vaccines).

For products without an existing safety specification, this section should provide information on the important identified and potential risks and important missing information associated with use of the product, based on pre- and post-authorization experience. Important identified and potential risks may include, for example:

- important adverse reactions;
- interactions with other medicinal products;
- interactions with foods and other substances;
- medication errors;
- effects of occupational exposure; and
- pharmacological class effects.

The summary on important missing information should consider whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

VII.B.5.16.2. PSUR/PBRER sub-section "Signal evaluation"

This sub-section of the PSUR/PBRER should summarize the results of evaluations of all safety signals that were closed (including SFDA requests of safety signal evaluation reports that were closed by MAH) during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a risk, following evaluation. The two main categories to be included in this sub-section are:

1. Those signals that, following evaluation, have been rejected as false signals based on a scientific evaluation of the currently available information.

2. Those signals that, following evaluation, have been categorized as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a sufficient description of each signal evaluation should be included in order to clearly describe the basis upon which the signal was either rejected or considered to be a risk by the MAH.

It is recommended that the level of detail provided in the description of the signal evaluation should reflect the medical significance of the signal (e.g. severe, irreversible, lead to increased morbidity or mortality) and potential public health importance (e.g. wide usage, frequency, significant use outside the recommendations of the product information) and the extent of the available evidence. Where multiple evaluations will be included under both categories of closed signals, they can be presented in the following order:

- Closed and refuted signals.
- Closed signals that are categorized as important potential risks.
- Closed signals that are categorized as important identified risks.
- Closed signals that are potential risks not categorized as important.
- Closed signals that are identified risks not categorized as important.

Where applicable the evaluations of closed signals can be presented by indication or population.

Each evaluation should include the following information as appropriate:

- source or trigger of the signal;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms (e.g., PTs, HLTs, SOCs, etc.) or Standardized MedDRA Queries (SMQs) that were reviewed), and analytical approaches;
- results - a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an individual case (e.g. an index case of well documented agranulocytosis or Stevens Johnson Syndrome);
- discussion;
- conclusion.

VII.B.5.16.3. PSUR/PBRER sub-section "Evaluation of risks and new information"

This sub-section should provide a critical appraisal of new information relevant to previously recognized potential and identified risks, together with an update on important missing information. New information that constitutes a signal with respect to a previously recognized risk or previously refuted signal should be evaluated in sub-section 16.2 ("Signal evaluation"). New information for evaluation in this sub-section of the PSUR/PBRER would generally include information that provides insight on a new aspect of a known risk, but which does not require further action to verify, for example new information from spontaneous reports leads to a labelling update with an associated MedDRA PT added but the risk is not categorized as important. Other examples could include new information that confirms a potential risk as an identified risk, information that indicates a change in frequency of a known risk, or information which allows any other further characterization of a previously recognized risk.
New information can be organized as follows:

1. New information on important potential risks.
2. New information on important identified risks.
3. New information on other potential risks not categorized as important.
4. New information on other identified risks not categorized as important.
5. Update on important missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PSUR/PBRER. This should be concise and interpret the impact, if any, on the understanding and characterization of the risk. Where applicable, the evaluation will form the basis for an updated characterization of important potential and identified risks in sub-section 16.4 ("Characterization of risks") of the report. It is recommended that the level of detail of the evaluation included in this sub-section should be proportional to the available evidence on the risk and its medical significance and public health relevance.
The evaluation(s) of the new information and missing information update(s) can be included in this sub-section of the PSUR/PBRER, or in an appendix. Each evaluation should include the following information as appropriate:

- source of the new information;

- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- results – a summary and critical analysis of the data considered in the risk evaluation;
- discussion;
- conclusion, including whether or not the evaluation supports an update of the characterization of any of the important potential and identified risks in sub-section 16.4 ("Characterization of risks")

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this sub-section. Unresolved concerns and uncertainties should be acknowledged.

VII.B.5.16.4. PSUR/PBRER sub-section "Characterization of risks"

This sub-section should characterize important identified and potential risks based on cumulative data (i.e., not restricted to the reporting interval), and describe important missing information.

Depending on the nature of the data source, the characterization of risk may include, where applicable:

- frequency;
- numbers of cases (numerator) and precision of estimate, considering the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk and precision of estimate;
- estimate of absolute risk and precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- patient characteristics relevant to risk (e.g., patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);
- dose, route of administration;

- duration of treatment, risk period;
- preventability (i.e., predictability, ability to monitor for a "sentinel" adverse reaction or laboratory marker);
- reversibility;
- potential mechanism; and
- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

For PSUR/PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- risks relating to the active substance;
- risks related to a specific formulation or route of administration (including occupational exposure);
- risks relating to a specific population;
- risks associated with non-prescription use (for compounds that are available as both prescription and non-prescription products); and
- safety concerns regarding missing information.

VII.B.5.16.5. PSUR/PBRER sub-section: "Effectiveness of risk minimization (if applicable)"

Risk minimization activities are public health interventions intended to prevent the occurrence of an ADR(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The aim of a risk minimization activity is to reduce the probability or severity of an ADR. 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 PSUR/PBRER shall contain the results of assessments of the effectiveness of risk minimization activities relevant to the benefit-risk assessment.

Relevant information on the effectiveness and/or limitations of specific risk minimization activities for important identified risks that has become available during the reporting interval should be summarized in this sub-section of the PSUR/PBRER.

Insights into the effectiveness of risk minimization activities that may be applicable across multiple regions are of particular interest. Information may be summarized by region, if applicable and relevant.

Additionally, results of evaluations that became available during the reporting interval, which refer to an individual country/region should be provided in the PSUR/PBRER regional appendix (see VII.B.5.20. and VII.C.5.6) to comply with national or regional requirements.

VII.B.5.17. PSUR/PBRER section "Benefit evaluation"

VII.B.5.17.1. PSUR/PBRER sub-section "Important baseline efficacy and effectiveness information"

This sub-section of the PSUR/PBRER summarizes information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval. This information should relate to authorized indication(s) of the medicinal product listed in the reference information.

For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterized separately by these factors when relevant.

When there have been no significant changes in the benefit or risk profile of the medicinal product in the reporting interval, the summary should be succinct, essentially the content of the reference information or included in the indications listed in the Introduction section of the PSUR/PBRER.

For medicinal products where there have been significant changes in either the risk or benefit profile, the sub-section should include sufficient information to support an updated characterization of the benefit of the medicinal product in PSUR/PBRER sub-section 17.3 ("Characterization of benefits") and the benefit-risk assessment in section 18 ("Integrated benefit-risk analysis for authorised indications"). The type and extent of the information presented will vary by product, and may include the following, if available and relevant:

- the epidemiology and natural history of the disease;
- nature of the benefit (e.g. diagnostic, preventive, symptomatic, or disease modifying treatment);

- important endpoints that support the benefit (e.g. effects on mortality, symptoms, patient reported outcomes);
- evidence of efficacy and effectiveness by comparator (e.g. active-controlled trials, meta-analyses, observational studies); and
- when relevant to the benefit-risk evaluation; trends, patterns and/or evidence of benefit in important subgroups, (e.g. age, sex, disease severity, or genetic polymorphism).

VII.B.5.17.2. PSUR/PBRER sub-section "Newly identified information on efficacy and effectiveness"

For some products, additional information on efficacy or effectiveness in authorized indications may have become available during the reporting interval. Such information should be presented in this sub-section of the PSUR/PBRER. Substantive information on evidence supporting use in unauthorized indications should not be included unless relevant for the benefit-risk evaluation in the authorized indications.

In this sub-section, particular attention should be given to vaccines, anti-infective agents or other medicinal products where changes in the therapeutic environment may impact on efficacy/effectiveness over time.

The type and extent of the information presented in this sub-section will vary by product and could refer to PSUR/PBRER sub-section 17.1 ("Important baseline efficacy and effectiveness information") if no new information became available.

VII.B.5.17.3. PSUR/PBRER sub-section "Characterization of benefits"

This sub-section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorized indications.

When there are no new relevant benefit data provided and no significant change in risk profile, this sub-section should refer to PSUR/PBRER sub-section 17.1 ("Important baseline efficacy and effectiveness information").

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.

When there is significant change to the risk profile or new evidence that suggests benefit is

significantly less than originally demonstrated, this section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy and effectiveness, considering the following when applicable:

- a brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
- new information that challenges the validity of a surrogate endpoint, if used;
- clinical relevance of the effect size;
- generalizability of treatment response across the indicated patient population (e.g., information that demonstrates lack of treatment effect in a sub-population);
- adequacy of characterization of dose-response;
- duration of effect;
- comparative efficacy; and
- a determination of the extent to which efficacy findings from clinical trials are generalizable to patient populations treated in medical practice.

VII.B.5.18. PSUR/PBRER section "Integrated benefit-risk analysis for authorized indications"

The MAH should provide in this PSUR/PBRER section an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. This section should provide an analysis and integration of the information in the previous sections with respect to benefit and risk and should not duplicate the benefit and risk information presented in sections 16.2 ("Signal evaluation"), 16.3 ("Evaluation of risks and new information") and 17.3 ("Characterization of benefits").

Whereas previous sections should include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections should be carried forward for integration in the benefit-risk evaluation.

VII.B.5.18.1. PSUR/PBRER sub-section "Benefit-risk context - medical need and important alternatives"

This sub-section of the PSUR/PBRER should provide a brief description of the medical need for the medicinal product in the authorized indications and summarized alternatives (medical, surgical or other; including no treatment).

VII.B.5.18.2. PSUR/PBRER sub-section "Benefit-risk analysis evaluation"

A benefit-risk profile is generally specific to an indication and population. Therefore, for products authorized for more than one indication, benefit-risk profile should usually be evaluated and presented by each indication individually. There may be some circumstances for products authorized for multiple indications (e.g. antibiotics) where it would be appropriate to assess the benefit-risk profile across more than one indication or population. If there are important differences in the benefit-risk profile among populations within an indication, the benefit-risk evaluation should be presented by population, if possible.

The benefit-risk evaluation should be presented in a structured manner as described below:

- General points regarding benefits and risks.
- Consider 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).
- With respect to benefit, consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g. for therapies for rheumatoid arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
- With respect to risk, consider its clinical importance, (e.g. nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients), and whether it arose from clinical trials in unauthorized indications or populations, off-label use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. For example, uncertainty in important benefits and/or risks

may reduce their contribution(s) to the evaluation. Limitations of the assessment should be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:

- The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation should be clear.
- Comment on the feasibility of expressing benefits and risks in such a way as to facilitate their comparison.
- If a formal quantitative assessment of benefit-risk is provided, a summary of the methods should be included.
- Economic considerations (e.g. cost-effectiveness) should not be considered in the benefit-risk evaluation.

When there is important new information or an ad hoc PSUR/PBRER has been requested, a detailed benefit-risk analysis based on cumulative data would be appropriate. Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

VII.B.5.19. PSUR/PBRER section "Conclusions and actions"

A PSUR/PBRER should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorized indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the MAH should assess the need for changes to the reference information/reference safety information and propose changes as appropriate.

In addition, and as applicable, the conclusions should include preliminary proposal(s) to optimize or further evaluate the benefit-risk balance for further discussion with the SFDA. This may include proposals for additional risk minimization activities.

For products with a pharmacovigilance or RMP, the proposals should be incorporated into pharmacovigilance planning together with the risk minimization plan (see Module V).

VII.B.5.20. Appendices to the PSUR/PBRER

A PSUR/PBRER should contain the following appendices as appropriate:

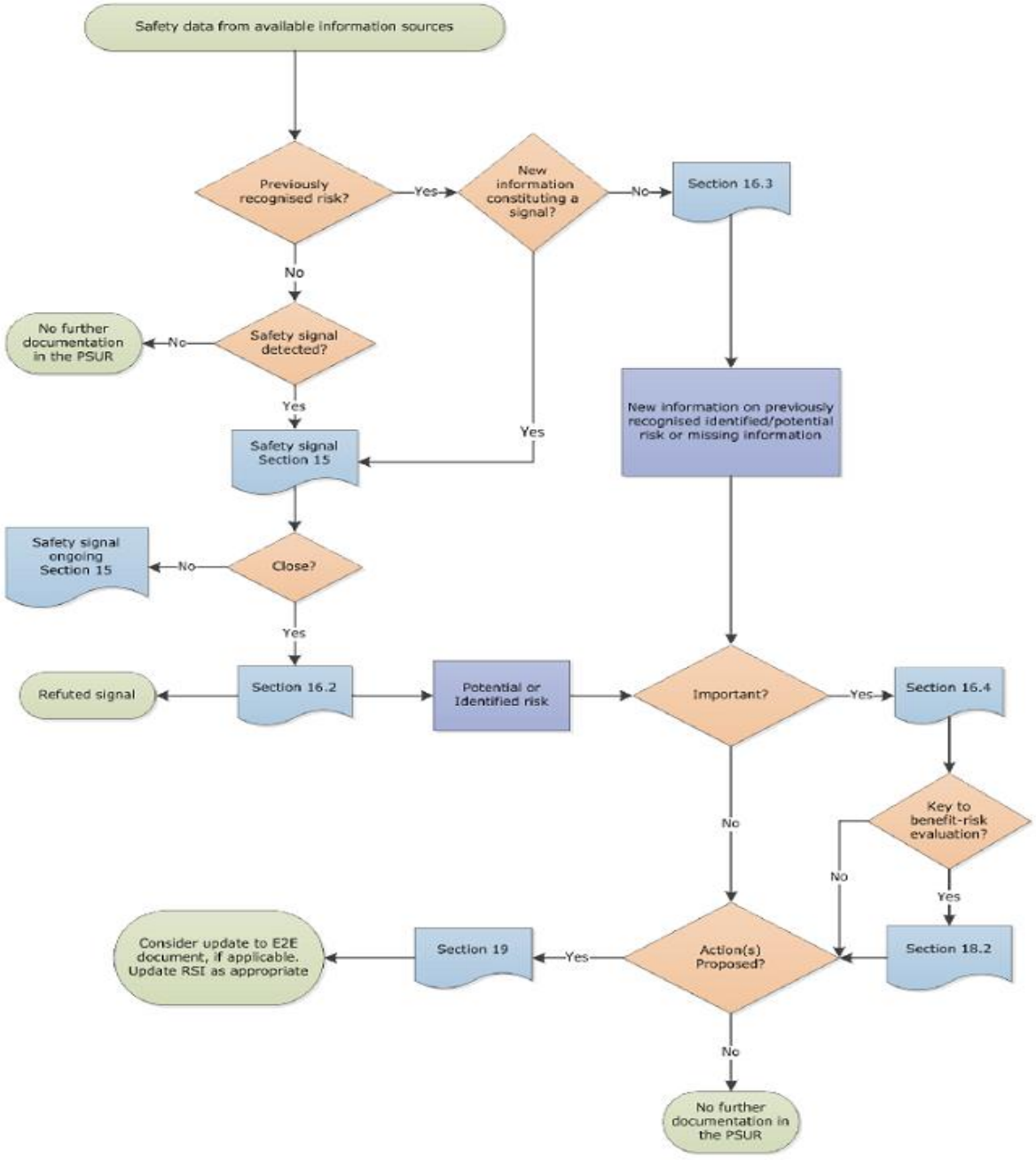
1. Reference information. See VII.B.4.
2. Cumulative summary tabulations of serious adverse events from clinical trials.
3. Cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources.
4. Tabular summary of safety signals.
5. Listing of all the MAH-sponsored interventional trials with the primary aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of the medicinal product.
6. Listing of all MAH-sponsored non-interventional studies conducted with the primary 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.
7. List of the sources of information used to prepare the PSUR/PBRER (when desired by the MAH).
8. Regional appendix:

The information included in this appendix should be used to comply with national or regional requirements.

VII.B.5.21. Mapping signals and risks to PSUR/PBRER sections/sub-sections

The following flowchart (Figure VII.1) reflects the general location for the presentation of information on signals and risks within the PSUR/PBRER.

Figure VII.1. PSUR/PBRER Sections/subsections – signals and risks.



VII.B.6. Quality systems for PSUR/PBRERs at the level of MAHs

MAHs should have in place structures and processes for the preparation, quality control, review and submission of PSUR/PBRERs including follow-up during and after their assessment. These structures and processes should be described by means of written policies and procedures in the MAH's quality system (see Module I).

There are a number of areas in the pharmacovigilance process that can directly impact the quality of PSUR/PBRERs, some examples are case management of spontaneous and study reports, literature screening, signal management, additional pharmacovigilance and post-marketing research activities, procedures for integration of information on benefits and risks from all available data sources and maintenance of product information. The quality system should describe the links between the processes, the communication channels and the responsibilities with the aim of gathering all the relevant information for the production of PSUR/PBRERs. There should be documented procedures including quality control checks in place to check the accuracy and completeness of the data presented in the PSUR/PBRERs. In ensuring completeness of data, a documented template or plan for drawing data from various data sources could be developed. The importance of an integrated approach to benefit-risk evaluation should underpin processes and cross departmental input to PSUR/PBRER preparation.

The PSUR/PBRER should also contain the assessment of specific safety issues requested by competent authorities (worldwide). The MAH should have mechanisms in place to ensure that the requests made by competent authorities (worldwide) during the time of their PSUR/PBRER assessment are properly addressed.

The provision of the data included in the summary tabulations (see VII.B.5.6.) should undergo source data verification against the MAH's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.

An appropriate quality system should be in place in order to avoid failure to comply with PSUR/PBRER requirements such as:

- non-submission: complete non-submission of PSUR/PBRERs, submission outside the correct submission schedule or outside the correct time frames (without previous agreement with the competent authorities);
- unjustified omission of information required by VII.B.5.;
- poor quality reports: poor documentation or insufficient information or evaluation provided to perform a thorough assessment of the new safety information, signals, risk evaluation, benefit evaluation and integrated benefit-risk analysis, misuse not highlighted,

absence of use of standardized medical terminology (e.g. MedDRA) and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;

- submission of a PSUR/PBRER where previous requests from competent authorities (worldwide) have not been addressed.

- failure to provide an explicit evaluation of the risk-benefit balance of the medicinal product;

- failure to provide adequate proposals for the local authorized product information.

Any significant deviation from the procedures relating to the preparation or submission of PSUR/PBRERs should be documented and the appropriate corrective and preventive action should be taken. This documentation should be available at all times.

When the preparation of the PSUR/PBRER is delegated to third parties, the MAH should ensure that they are subject to a quality system compliant with the current legislation. Explicit procedures and detailed agreements should exist between the MAH and third parties. The agreements may specifically detail the options to audit the PSUR/PBRER preparation process.

VII.B.7. Training of staff members related to the PSUR/PBRER process

For all organizations, it is the responsibility of the person responsible for the pharmacovigilance system to ensure that the personnel, including pharmacovigilance, medical and quality personnel involved in the preparation, review, quality control, submission and assessment of PSUR/PBRERs are adequately qualified, experienced and trained according to the applicable guidelines (e.g. ICH E2C(R2) and this GVP Module VII). When appropriate, specific training for the different processes, tasks and responsibilities relating to the PSUR/PBRER should be in place.

Training to update knowledge and skills should also take place as necessary.

Training should cover legislation, guidelines, scientific evaluation and written procedures related to the PSUR/PBRER process. Training records should demonstrate that the relevant training was delivered prior to performing PSUR/PBRER-related activities.

VII.C. OPERATION WITHIN KSA

VII.C.1. Standard submission schedule of PSUR/PBRERs

MAHs shall submit PSUR/PBRERs according to the following submission schedule (hereafter "standard" submission schedule):

- At 6 months intervals once the product is authorized, even if it is not marketed;
- Once a product is marketed, and based on the product international birth date, a 6 monthly PSUR/PBRER submission should be continued following initial placing on the market in the KSA for 2 years, then once a year for the following 2 years and thereafter at 3-yearly intervals.
- The submission of PSUR/PBRERs in accordance with the European Union reference date (EURD) list and frequencies is also acceptable.

- The MAH should submit the PSUR/PBRER in CD or via DS@sfda.gov.sa for medicinal product authorized in Saudi Arabia that contains a new chemical entity, biological/biosimilar medicinal products and first registered generics.

- The MAH should submit the PSUR/PBRER submission plan annually via DS@sfda.gov.sa for medicinal product authorized in Saudi Arabia that contains a new chemical entity, biological/biosimilar medicinal products and first registered generics.

VII.C.2. Application of the submission of PSUR/PBRERs

VII.C.2.1 Submission of PSUR/PBRERs for fixed dose combination products

If the substance that is the subject of the PSUR/PBRER is also authorized as a component of a fixed combination medicinal product, the MAH shall either submit a separate PSUR/PBRER for the combination of active substances authorized for the same MAH with cross-references to the single-substance PSUR/PBRER(s) or provide the combination data within one of the single-substance PSUR/PBRERs.

VII.C.2.2. Submission of PSUR/PBRERs on demand of the SFDA

MAHs shall submit PSUR/PBRERs immediately upon request from the SFDA. When the

timeline for submission has not been specified in the request, MAHs should submit the PSUR/PBRER within 90 calendar days of the data lock point.

VII.C.3. PSUR/PBRER and risk management plan – common modules

The proposed modular formats for the PSUR/PBRER and the RMP aim to address duplication and facilitate flexibility by enabling common PSUR/PBRER/RMP sections to be utilized interchangeably across both reports. Common sections with the above-mentioned reports are identified in Table VII.1.:

Common sections between RMP and PSUR/PBRER (may not be in identical format)

RMP section	PSUR/PBRER section
Part II, module SV – "Post-authorization experience", section "Regulatory and MAH action for safety reason"	Section 3 – "Actions taken in the reporting interval for safety reasons"
Part II, module SV – "Post-authorization experience", section "Non-study post-authorization exposure"	Sub-section 5.2 – "Cumulative and interval patient exposure from marketing experience"
Part II, Module SVII – "Identified and potential risks"	Sub-section 16.4 – "Characterization of risks"
Part II, module SVIII – "Summary of the safety concerns" (as included in the version of the RMP which was current at the beginning of the PSUR/PBRER reporting interval)	Sub-section 16.1 – "Summary of safety concerns"
Part V – "Risk minimization measures", section "Evaluation of the effectiveness of risk minimization activities"	Sub-section 16.5 – "Effectiveness of risk minimization (if applicable)"

VII.C.4. KSA specific requirements for periodic safety update reports

The scientific evaluation of the benefit-risk balance of the medicinal product included in the

PSUR/PBRER detailed in VII.B.5. shall be based on all available data, including data from clinical trials in unauthorized indications and populations.

MAHs should submit below additional requirements:

1- Sub-section "KSA-approved product information":

This sub-section should contain the latest approved version of product information (SPC/ PIL).

2- Sub-section "Proposed product information":

This sub-section should include the proposed amendments to the SPC/PIL with track changes feature based on the assessment of the current PSUR/PBRER. All necessary documentation that support such amendments should be provided.

3- Sub-section "Proposed additional pharmacovigilance and/or risk minimization activities":

This sub-section should include any proposal for additional pharmacovigilance and/or additional risk minimization activities based on PSUR/PBRER assessment.

4- Sub-section: Patient exposure in the KSA:

This section should provide information about the cumulative and interval patient exposure in the KSA only.

5- Sub-section: ADRs reporting in the KSA:

This sub-section should provide a summary tabulation of all received ADRs in the KSA (from all available sources) during the reporting interval and cumulatively.

6- Sub-section: Clinical trials in the KSA:

This section should list all clinical trials during the reporting interval and cumulatively, either planned, ongoing or completed.

VII. APPENDIX 1. EXAMPLES OF TABULATIONS FOR ESTIMATED EXPOSURE AND ADVERSE EVENTS/REACTIONS DATA

MAHs can modify these examples tabulations to suit specific situations, as appropriate.

Table VII.2. Estimated cumulative subject exposure from clinical trials

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomization schemes for ongoing trials.

Treatment	Number of Subjects
Medicinal product	
Comparator	
Placebo	

Table VII.3. Cumulative subject exposure to investigational drug from completed clinical trials by age and sex

Number of subjects			
Age range	Male	Female	Total

Data from completed trials as of <insert date>

Table VII.4. Cumulative subject exposure to investigational drug from completed clinical trials by racial/ethnic group

Racial/ethnic group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

Data from completed trials as of <insert date>

Table VII.5. Cumulative exposure from marketing experience

Indication	Sex		Age (years)				Dose			Formulation		Region					
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	Arab country concerned	EU	Japan	Colombia	US/Canada	Other
Overall																	
e.g. Depression																	
e.g. Migraine																	

Table VII.5 includes cumulative data obtained from day/month/year throughout day/month/year, where available.

Table VII.6. Interval exposure from marketing experience

Indication	Sex		Age (years)				Dose			Formulation		Region					
	Male	Female	2 to ≤16	>16 to 65	>65	Unknown	<40	≥40	Unknown	Intravenous	Oral	Arab country concerned	EU	Japan	Colombia	US/Canada	Other
e.g. Depression																	
e.g. Migraine																	

Table VII. 6 includes interval data obtained from day/month/year throughout day/month/year

Table VII.7. Cumulative tabulation of serious adverse events from clinical trials

System Organ Class Preferred Term	**Investigational medicinal product**	**Blinded**	**Active comparator**	**Placebo**
Blood and lymphatic system disorders				
Anemia				
Cardiac disorders				
Tachycardia				
<SOC>				
<PT>				

Table VII.8. Numbers of adverse reactions by preferred term from post-authorization sources*

MedDRA SOC PT	**Spontaneous, including medicines authorities (worldwide) and literature**					**Non-interventional post-marketing study and reports from other solicited sources ****	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
<SOC 1>							
<PT>							
<SOC 2>							
<PT>							

* Non-interventional post-authorization studies, reports from other solicited sources and spontaneous ICSRs (i.e., reports from healthcare professionals, consumers, medicines authorities (worldwide), and scientific literature)

** This does not include interventional clinical trials.

VII. APPENDIX 2. EXAMPLE OF TABULAR SUMMARY OF SAFETY SIGNALS THAT WERE ONGOING OR CLOSED DURING THE REPORTING INTERVAL

Table VII.9. The tabular summary below is a fictitious example of tabular summary of safety signals ongoing or closed during the reporting interval

Reporting interval: DD-MMM-YYYY to DD-MMM-YYYY

Signal term	Date detected	Status (ongoing or closed)	Date closed(for closed signals)	Source of signal	Reason for evaluation and summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	MMM/YYYY	Ongoing	MMM/YYYY	Meta-analysis (published trial)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
SJS	MMM/YYYY	closed	MMM/YYYY	Spontaneous case reports	Rash already identified risk SJS not reported in preauthorization CTs 4 reports within 6 months of authorization; plausible time to onset and no possible alternative causes	Targeted follow up of reports with site visit to one hospital. Full review of cases by MAH, dermatologist and literature searches	RSI updated with a warning and precaution DHPC sent Effectiveness survey planned 6 months post DHPC. RMP updated

Explanatory notes:

Signal term:

A brief descriptive name of a medical concept for the signal. This may evolve and be refined as the signal is evaluated. The concept and scope may or may not be limited to specific MedDRA term(s), depending on the source of signal.

Date detected:

Month and year the MAH became aware of the signal.

Status:

Ongoing: Signal under evaluation at the data lock point of the PSUR/PBRER. Anticipated completion date,

if known, should be provided.

Closed: Signal for which evaluation was completed before the data lock point of the PSUR/PBRER.

Note: A new signal of which the MAH became aware during the reporting interval may be classified as closed or ongoing, depending on the status of the signal evaluation at the end of the reporting interval of the PSUR/PBRER.

Date closed:

Month and year when the signal evaluation was completed.

Source of signal:

Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous reports, clinical trial data, scientific literature, and non-clinical study results, or information request or inquiries from a medicines authority (worldwide).

Reason for evaluation and summary of key data:

A brief summary of key data and rationale for further evaluation.

Action(s) taken or planned:

State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the data lock point, these should be listed, otherwise leave blank for ongoing signals.

VII.APPENDIX 3. TEMPLATE FOR COVER PAGE FOR PSUR/PBRER SUBMISSION

PERIODIC SAFETY UPDATE REPORT

for

ACTIVE SUBSTANCE(S): <INN>

ATC CODE(S): <Code(s)>

MEDICINAL PRODUCTS COVERED:

Invented Name of the Medicinal Product(s)	Marketing Authorization Number(s)	Date(s) of Authorization	Marketing Authorization Holder
<>	<>	<>	<>
<>	<>	<>	<>

INTERNATIONAL BIRTH DATE (IBD): <Date>

OTHER INFORMATION:

<Other identifying or clarifying information if necessary>

MAH'S NAME AND ADDRESS:

<Name>

<Address>

<E-mail address> **(contact person for the PSUR/PBRER procedure)**

NAME AND CONTACT DETAILS OF THE QPPV:

<Name>

<Address>

<Telephone number>

<Fax number>

<E-mail address>

SIGNATURE (QPPV or designated person): <Signature>

Annex 1

Format of PSUR/PBRERs

1. Electronic PSUR/PBRERs shall be submitted in the format set out in Annex II.
2. The Agency may publish templates for the modules set out in Annex II.

Annex II

Format of the electronic PSUR/PBRERs

The PSUR/PBRER shall consist of the following modules:

Part I Title page including signature

Part II Executive Summary

Part III Table of contents

1. Introduction
2. Worldwide marketing authorization status
3. Actions taken in the reporting interval for safety reasons
4. Changes to reference safety information
5. Estimated exposure and use patterns
   5.1. Cumulative subject exposure in clinical trials
   5.2. Cumulative and interval patient exposure from marketing experience
6. Data in summary tabulations
   6.1. Reference information
   6.2. Cumulative summary tabulations of serious adverse events from clinical trials
   6.3. Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting interval
   7.1. Completed clinical trials
   7.2. Ongoing clinical trials
   7.3. Long-term follow-up
   7.4. Other therapeutic use of medicinal product
   7.5. New safety data related to fixed combination therapies
8. Findings from non-interventional studies
9. Information from other clinical trials and sources
10. Non-clinical data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information EN

15. Overview on signals: New, ongoing or closed
16. Signal and risk evaluation
    16.1. Summaries of safety concerns
    16.2. Signal evaluation
    16.3. Evaluation of risks and new information
    16.4. Characterization of risks
    16.5. Effectiveness of risk minimization (if applicable)
17. Benefit evaluation
18. Important baseline efficacy and effectiveness information
19. Newly identified information on efficacy and effectiveness
20. Characterization of benefits
21. Integrated benefit-risk analysis for authorized indications
    21.1. Benefit-risk context — Medical need and important alternatives
    21.2. Benefit-risk analysis evaluation
22. Conclusions and actions
23. Appendices to the PSUR/PBRER

Module VIII – Post-authorization Safety Studies

VIII.A. 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 MAH voluntarily, or pursuant to an obligation imposed by the SFDA. This Module concerns PASS which are interventional or non-interventional studies and does not address pre-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; and
- 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 collection of blood samples may be performed as part of normal clinical practice.

If a PASS is a clinical trial, other SFDA guidelines should be followed (Regulation and Requirements for Conducting Clinical Trials on Drug, Good Clinical Practice Guidelines).

The purposes of this Module are to:

- provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by MAHs (VIII.B.);
- describe procedures whereby the SFDA may impose to a MAH an obligation to conduct a clinical trial or a non-interventional study (VIII.C.), 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 (VIII.C.).

The guidance in VIII.B. applies to non-interventional PASS which are initiated, managed or financed by a MAH and conducted in the KSA. This guidance should also be used for studies conducted outside the KSA which have been imposed or required by the SFDA. In VIII.B., some legal requirements which are applicable to studies conducted pursuant to an obligation are recommended to all PASS in order to support the same level of transparency, scientific standards and quality standards for all PASS. This applies, for example, to the format and content of study protocols, abstracts and final study reports. A distinction is made in the text between situations where the provision of the guidance represents a legal requirement or a recommendation.

This guidance applies to studies initiated, managed or financed by a MAH as well as those conducted by a third party on behalf of the MAH. This guidance applies to studies that involve primary collection of safety data directly from patients and healthcare professionals and those that make secondary use of data previously collected from persons and healthcare professionals for another purpose.

VIII.A.1. Terminology

Date at which a study commences: date of the start of data collection.

Start of data collection: the date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts. Simple counts in a database to support the development of the study protocol, for example to inform the sample size and statistical precision of the study, are not part of this definition.

End of data collection: the date from which the analytical dataset is completely available.

Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

Substantial amendment to the study protocol: amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, the study population, the sample size, the study design, the data sources, the method of data collection, the definitions of the main exposure, outcome and confounding variables and the statistical analytical plan.

VIII.B. Structures and processes

VIII.B.1. Principles

A post-authorization study should be classified as a PASS when the main aim for initiating the study includes any of the following objectives:

- to quantify potential or identified risks, e.g. to characterize the incidence rate, estimate the rate ratio or rate difference in comparison to a non-exposed population or a population exposed to another medicinal product, class of medicinal products or other intervention as appropriate, and investigate risk factors, including effect modifiers;
- to evaluate risks of a medicinal product used in patient populations for which safety information is limited or missing (e.g. pregnant women, specific age groups, patients with renal or hepatic impairment or other relevant comorbidity or co-medication);
- to evaluate the risks of a medicinal product after long-term use;
- to provide evidence about the absence of risks;
- to assess patterns of drug utilization that add knowledge regarding the safety of the medicinal product or the effectiveness of a risk management measure (e.g. collection of information on indication, off-label use, dosage, co-medication or medication errors in clinical practice that may influence safety, as well as studies that provide an estimate of the public health impact of any safety concern);
- to measure the effectiveness of a risk minimization activity.

If the study fulfils the above mention objectives, the classification of a post-authorization study as a PASS is not constrained by the type of design chosen if it fulfils the criteria. For

example, a systematic literature review or a meta-analysis may be considered as PASS depending on their aim.

Relevant scientific guidance should be considered by MAHs and investigators for the development of study protocols, the conduct of studies and the writing of study reports, and by the SFDA for the evaluation of study protocols and study reports. Relevant scientific guidance includes ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, the Guideline on Conduct of Pharmacovigilance for Medicines Used by Pediatric Population, and Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP).

For studies that are funded by a MAH, including studies developed, conducted or analyzed fully or partially by investigators who are not employees of the MAH, the MAH should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the MAH and investigators should ensure that the study meets its regulatory obligations while permitting their scientific expertise to be exercised throughout the research process. In the research contract, the MAH should consider the provisions of the ENCePP Code of Conduct, and address the following aspects:

- rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
- rights and obligations of the investigator(s) and MAH;
- clear assignment of tasks and responsibilities;
- procedure for achieving agreement on the study protocol;
- provisions for meeting the MAH's pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable;
- intellectual property rights arising from the study and access to study data;
- storage and availability of analytical dataset and statistical programs for audit and inspection;
- communication strategy for the scheduled progress and final reports;
- publication strategy of interim and final results.

Non-interventional post-authorization safety studies shall not be performed where the act of conducting the study promotes the use of a medicinal product. This requirement applies to all

studies and to all activities performed in the study, including for studies conducted by the personnel of the MAH and by third parties on behalf of the MAH.

Payments to healthcare professionals for participating shall be restricted to compensation for time and expenses incurred.

VIII.B.2. Study registration

Non interventional PASS should be registered at the SFDA before the study commences or at the earliest possible date, for example if data collection had already started for a study included in the RMP. The study protocol should be submitted to SFDA as soon as possible after its finalization and prior to the start of data collection. Updated study protocols in case of substantial amendments, progress reports and the final study report should also be SFDA (as soon as possible and preferably within two weeks after their finalization). Study information should normally be submitted in English. If the study protocol or the study report is written in another language, the marketing authorization should facilitate access to study information by including an English translation of the title, the abstract of the study protocol and the abstract of the final study report.

VIII.B.3. Study protocol

All non-interventional PASS must have a written study protocol before the study commences. The study should follow a scientifically sound protocol developed by individuals with appropriate scientific background and experience. The KSA requirements shall be followed for ensuring the well-being and rights of the participants. The MAH may be required by the SFDA to submit the protocol.

For PASS initiated by the MAH pursuant to an obligation, see VIII.C.2 for the submission of the study protocol.

In order to ensure compliance of the MAH with its pharmacovigilance obligations, the QPPV or his/her delegate (see Module I) should be involved in the review and sign-off of study protocols conducted in the KSA.

VIII.B.3.1. Format and content of the study protocol

The study protocol should include the following information:

1. **Title**: informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned, and a sub-title with a version identifier and the date of the last version.
2. **MAH**: name and address of the MAH.
3. **Responsible parties**: names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the SFDA upon request.
4. **Abstract**: stand-alone summary of the study protocol including the following sub-sections:
    - Title with subtitles including version and date of the protocol and name and affiliation of main author
    - Rationale and background
    - Research question and objectives
    - Study design
    - Population
    - Variables
    - Data sources
    - Study size
    - Data analysis
    - Milestones
5. **Amendments and updates**: any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to the section of the protocol where the change has been made.
6. **Milestones: table with planned dates for the following milestones:**
    - Start of data collection
    - End of data collection
    - Study progress report(s)
    - Interim report(s) of study results, where applicable, in line with phases of data analyses

- Final report of study results

Any other important timelines in the conduct of the study should be presented.

7. **Rationale and background:** short description of the safety hazard(s), the safety profile or the risk management measures that led to the initiation or imposition of the study, and short critical review of available published and unpublished data to explain gaps in knowledge that the study is intended to fill. The review may encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The review should cite the findings of similar studies, and the expected contribution of the current study.
8. **Research question and objectives:** research question that explains how the study will address the issue which led to the study being initiated or imposed, and research objectives, including any pre-specified hypotheses and main summary measures.
9. **Research methods:** description of the research methods, including:
   9.1. **Study design**: overall research design and rationale for this choice.
   9.2. **Setting**: study population defined in terms of persons, place, time period, and selection criteria, including the rationale for any inclusion and exclusion criteria and their impact on the number of subjects available for analysis. Where any sampling from a source population is undertaken, description of the source population and details of sampling methods should be provided. Where the study design is a systematic review or a meta-analysis, the criteria for the selection and eligibility of studies should be explained.
   9.3. **Variables**: outcomes, exposures and other variables including measured risk factors should be addressed separately, including operational definitions; potential confounding variables and effect modifiers should be specified.
   9.4. **Data sources**: strategies and data sources for determining exposures, outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers. Where the study will use an existing data source, such as electronic health records, any information on the validity of the recording and coding of the data should be reported. If data collection methods or instruments are tested in a pilot study, plans for the pilot study should be presented. If a pilot study has already been performed, a summary of the results should be reported.

Involvement of any expert committees to validate diagnoses should be stated. In case of a systematic review or meta-analysis, the search strategy and processes and any methods for confirming data from investigators should be described.

9.5. **Study size**: any projected study size, precision sought for study estimates and any calculation of the sample size that can minimally detect a pre-specified risk with a pre-specified statistical precision.

9.6. **Data management**: data management and statistical programs to be used in the study, including procedures for data collection, retrieval and preparation.

9.7. **Data analysis**: the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, impute values, modify raw data, categorize, analyze and present results, and procedures to control sources of bias and their influence on results; statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or association, and sensitivity analyses.

9.8. **Quality control**: description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of statistical programs. As appropriate, certification and/or qualifications of any supporting laboratory or research groups should be included.

9.9. **Limitations of the research methods:** any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalizability, and random error. The likely success of efforts taken to reduce errors should be discussed.

10. **Protection of human subjects:** safeguards in order to comply with the SFDA for ensuring the well-being and rights of participants in non-interventional post-authorization safety studies.

11. **Management and reporting of adverse events/adverse reactions:** procedures for the collection, management and reporting of individual cases of suspected adverse reactions and of any new information that might influence the evaluation of the benefit-risk balance of the product while the study is being conducted.

For studies where information on certain adverse events will not be collected (see GVP

Module VI), the MAH should provide a justification for the overall approach to the collection of safety data in the protocol. Any reference to adverse events should be made using the appropriate level of the MedDRA classification (see GVP Annex IV). In case where information on certain adverse events will not be collected, this section should describe the channels and documents to be used to inform the healthcare professionals and consumers of the possibility to report adverse reactions to the MAH or to the national spontaneous reporting system (see GVP Module VI). In certain circumstances where suspected adverse reactions with fatal outcome will not be subject to expedited reporting as ICSRs (see GVP Module VI), each of these adverse reactions should be listed in a table using the appropriate level of the MedDRA classification with a rationale for not reporting them.

12. **Plans for disseminating and communicating study results,** including any plans for submission of progress reports and final reports.
13. **References.**

Feasibility studies that were carried out to support the development of the protocol, for example, the testing of a questionnaire or simple counts of medical events or prescriptions in a database to determine the statistical precision of the study, should be reported in the appropriate section of the study protocol with a summary of their methods and results. The full report should be made available to the SFDA upon request. Feasibility studies that are part of the research process should be described in the protocol, for example, a pilot evaluation of the study questionnaire(s) used for the first set of patients recruited into the study.

An annex should list all separate documents and list or include any additional or complementary information on specific aspects not previously addressed (e.g. questionnaires, case report forms), with clear document references.

VIII.B.3.2. Substantial amendments to the study protocol

The study protocol should be amended and updated as needed throughout the course of the study. Any substantial amendments to the protocol after the study start should be documented in the protocol in a traceable and auditable way including the dates of the changes. If changes to the protocol lead to the study being considered an interventional clinical trial, the SFDA should be informed immediately.

VIII.B.4. Reporting of pharmacovigilance data to the SFDA

VIII.B.4.1. Data relevant to the benefit-risk balance of the product

The MAH shall monitor the data generated while the study is being conducted and consider their implications for the benefit-risk balance of the medicinal product concerned. Any new information that may affect the benefit-risk balance of the medicinal product should be communicated immediately in writing as an Emerging Safety Issue to the SFDA. Information affecting the benefit-risk balance of the medicinal product may include that arising from an analysis of adverse reactions and aggregated data.

This communication should not affect information on the results of studies which should be provided by means of PSUR/PBRERs (see Module VII) and in RMP updates (see Module V), where applicable.

VIII.B.4.2. Reporting of adverse reactions/adverse events

Adverse reactions/adverse events should be reported to the SFDA in accordance with the provisions of Module VI. Procedures for the collection, management (including a review by the MAH if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarized in the study protocol. If appropriate, reference can be made to the PSMF (see Module II) but details specific to the study should be described in this section. For study designs where expedited reporting is not required, this should be stated in the study protocol.

VIII.B.4.3. Study reports

VIII.B.4.3.1 Progress reports

Progress reports may be requested by the SFDA. Requests for progress reports may be made before the study commences or any time during the study conduct. They may be guided by the communication of benefit-risk information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product.

The timing of the submission of progress reports should be agreed with the SFDA and specified in the study protocol when they have been agreed before the study commences. Study progress should also be reported in any PSUR/PBRERs (see Module VII) and RMP updates (see Module V), where applicable. This does not preclude the submission of the final study report separately for formal assessment.

The content of the progress report should follow a logical sequence and should include all the available data that are judged relevant for the progress of the study, for example, number of patients who have entered the study, number of exposed patients or number of patients presenting the outcome, problems encountered and deviations from the expected plan. The progress report may also include any interim report of study results. After review of the report, additional information may be requested.

VIII.B.4.3.2. Final study report

The final study report should be submitted as soon as possible within 12 months of the end of data collection.

If a study is discontinued, a final report should be submitted and the reasons for terminating the study should be provided.

The final study report should include the following information:

1. **Title**: title including a commonly used term indicating the study design; sub-titles with date of final report and name and affiliation of main author. If the study has been registered in the Saudi clinical trial registry, the final study report should mention on the title page "the Saudi clinical registry number:" with the registration number and the link to the study record.

2. **Abstract**: stand-alone summary in the format presented below.

3. **MAH**: name and address of the MAH.

4. **Investigators**: names, titles, degrees, addresses and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators should be made available to the SFDA.

5. **Milestones**: planned and actual dates for the following milestones:

   - Start of data collection
   - End of data collection or date of early termination, if applicable, with reasons for termination
   - Study progress report(s)

- Interim report(s) of study results, where applicable
- Final report of study results
- Any other important milestone applicable to the study, including date of protocol approval by an Institutional Review Board/Independent Ethics Committee if applicable, and date of study registration in the SFDA.

6. **Rationale and background:** short description of the safety concern(s) that led to the study being initiated or imposed, and short critical review of relevant published and unpublished data evaluating pertinent information and gaps in knowledge that the study is intended to fill.

7. **Research question and objectives:** research question and research objectives, including any pre-specified hypotheses, as stated in the study protocol.

8. **Amendments and updates to the protocol:** list of any substantial amendment and update to the initial study protocol after the start of data collection, including a justification for each amendment or update.

9. **Research methods:**

9.1. **Study design**: key elements of the study design and the rationale for this choice.

9.2. **Setting**: setting, locations, and relevant dates for the study, including periods of recruitment, follow-up, and data collection. In case of a systematic review or meta-analysis, study characteristics used as criteria for eligibility, with rationale.

9.3. **Subjects**: any source population and eligibility criteria of study subjects. Sources and methods of selection of participants should be provided, including, where relevant methods for case ascertainment, as well as number of and reasons for dropouts.

9.4. **Variables**: all outcomes, exposures, predictors, potential confounders, and effect modifiers, including operational definitions and diagnostic criteria, if applicable.

9.5. **Data sources and measurement**: for each variable of interest, sources of data and details of methods of assessment and measurement. If the study has used an existing data source, such as electronic health records, any information on the validity of the

recording and coding of the data should be reported. In case of a systematic review or meta-analysis, description of all information sources, search strategy, methods for selecting studies, methods of data extraction and any processes for obtaining or confirming data from investigators.

9.6. **Bias**: any efforts to assess and address potential sources of bias.

9.7. **Study size**: study size, rationale for any sample size calculation and any method for attaining projected study size.

9.8. **Data transformation**: transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

9.9. **Statistical methods**: description of:

- main summary measures
- statistical methods applied to the study, including those used to control for confounding and, for meta-analyses, methods for combining results of studies
- any methods used to examine subgroups and interactions
- how missing data were addressed
- any sensitivity analyses
- any amendment to the plan of data analysis included in the study protocol, with a rationale for the change.

9.10. **Quality control:** mechanisms to ensure data quality and integrity.

10. **Results**: presentation of tables, graphs, and illustrations to present the pertinent data and reflect the analyses performed. Both unadjusted and adjusted results should be presented. Precision of estimates should be quantified using confidence intervals. This section should include the following sub-sections:

10.1. **Participants**: numbers of study subjects at each stage of study, e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed, and reasons for non-participation at any stage. In the case of a systematic review or meta-analysis, number of studies screened,

assessed for eligibility and included in the review with reasons for exclusion at each stage.

10.2. **Descriptive data:** characteristics of study participants, information on exposures and potential confounders and number of participants with missing data for each variable of interest. In case of a systematic review or meta-analysis, characteristics of each study from which data were extracted (e.g. study size, follow-up).

10.3. **Outcome data:** numbers of participants across categories of main outcomes.

10.4. **Main results:** unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). If relevant, estimates of relative risk should be translated into absolute risk for a meaningful time period.

10.5. **Other analyses:** other analyses done, e.g. analyses of subgroups and interactions, and sensitivity analyses.

10.6. **Adverse events and adverse reactions:** summary of all adverse events/adverse reactions reported in the study, in line with requirements described in Module VI. For certain study designs with secondary use of data such as case-control or retrospective cohort studies, particularly those involving electronic healthcare records, systematic reviews and meta-analyses where it is not feasible to make a causality assessment at the individual case level, this should be stated.

11. **Discussion**:

11.1. **Key results:** key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed PASS, and, where relevant, impact of the results on the benefit-risk balance of the product.

11.2. **Limitations:** limitations of the study considering circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases should be discussed.

11.3. **Interpretation:** interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies and other relevant evidence.

11.4. **Generalizability:** the generalizability (external validity) of the study results.

12. Conclusions: main conclusions of the study deriving from the analysis of the data.

13. **References**.
14. **Other information**: any additional or complementary information on specific aspects not previously addressed.

The abstract of the final study report should include a summary of the study methods and findings presented in the following format:

1. Title, with subtitles including date of the abstract and name and affiliation of main author;
2. Keywords (not more than five keywords indicating the main study characteristics);
3. Rationale and background;
4. Research question and objectives;
5. Study design;
6. Setting;
7. Subjects and study size, including dropouts;
8. Variables and data sources;
9. Results;
10. Discussion (including, where relevant, an evaluation of the impact of study results on the benefit-risk balance of the product);
11. Conclusion
12. MAH;
13. Names and affiliations of principal investigators.

VIII.B.5. Publication of study results

For studies that are fully or partially conducted by investigators who are not employees of the MAH, the MAH and the investigator should agree in advance a publication policy allowing the principal investigator to independently prepare publications based on the study results irrespective of data ownership. The MAH should be entitled to view the results and interpretations included in the manuscript and provide comments prior to submission of the manuscript for publication.

VIII.B.5.1. submission of manuscripts accepted for publication

In order to allow the SFDA to review in advance the results and interpretations to be published, the MAH initiating, managing or financing a non-interventional PASS should

communicate to the SFDA within two weeks after first acceptance for publication.

VIII.B.6. Data protection

The national legislation and guidance on data protection must be followed.

For PASS imposed as an obligation, the MAH shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected.

VIII.B.7. Quality systems, audits and inspections

The MAH shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the MAH shall ensure that the analytical dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection. This provision should be applied for all PASS.

VIII.B.8. Impact on the risk management system

Non-interventional PASS imposed as an obligation should be included in the RMP as described in Module V.

VIII.C. Operation within the KSA

VIII.C.1. Procedure for imposing post-authorization safety studies

The conduct of any PASS can be imposed during the evaluation of the initial marketing authorization application or during the post-authorization phase by the SFDA whenever there are concerns about the risks of an authorized medicinal product. This obligation shall be duly justified and shall be notified in writing and shall include the objectives and timeframe for the submission and conduct of the study. The request should be based on benefit-risk considerations. The request may also include recommendations on key elements of the study (e.g. study design, setting, exposure(s), outcome(s), study population).

VIII.C.1.1. Request for a PASS as part of the initial marketing authorization application

A marketing authorization may be granted by the SFDA subject to the conduct of a PASS.

VIII.C.1.2. Request for a PASS during a post-authorization regulatory procedure

The need for a PASS could be identified by the SFDA during a post-authorization regulatory procedure, for example, an extension or a variation to a marketing authorization or a renewal procedure.

VIII.C.1.3. Request for a PASS due to an emerging safety concern

After the granting of the marketing authorization, the SFDA, may impose on the MAH an obligation to conduct a PASS if there are concerns about the risk of the authorized medicinal product.

VIII.C.1.4 Joint post-authorization safety studies

If safety concerns apply to more than one medicinal product, the SFDA, encourage the MAHs concerned to conduct a joint PASS. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the MAHs should contain the justification for the request of a joint study and may include core elements for the study protocol. Upon request from the MAHs, the SFDA may provide suggestions for a joint study proposal and facilitate agreement in developing a joint protocol.

VIII.C.1.5. Written observations in response to the imposition of an obligation

Within 30 days of receipt of the written notification of an obligation imposed after the granting of a marketing authorization, the MAH may request the opportunity to present written observations in response to the imposition of the obligation. The SFDA shall specify a time limit for the provision of these observations. On the basis of the written observations submitted by the MAH, the SFDA shall withdraw or confirm the obligation. When the obligation is confirmed, the marketing authorization shall be subject to variation to include the obligation as a condition and the RMP, where applicable, shall be updated accordingly (see Module V).

VIII.C.2. Supervision of non-interventional post-authorization safety studies conducted pursuant to an obligation

VIII.C.2.1. Roles and responsibilities of the MAH

The MAH shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this fulfilment can be audited, inspected and verified. Following the imposing as a condition to the marketing authorization to conduct a non-interventional PASS, the MAH shall develop a study protocol and submit it to the SFDA for review. The MAH has the responsibility to ensure that the study is not a clinical trial.

The MAH shall develop the study protocol following recommendations set out in this module. The study may commence only when the written endorsement from the SFDA has been issued.

After a non-interventional imposed PASS has been commenced, the MAH shall submit any substantial amendments to the protocol, before their implementation, to the SFDA.

Upon completion of the study, the MAH shall submit a final study report, including a public abstract, to the SFDA as soon as possible and not later than 12 months after the end of data collection.

VIII.C.2.2. Roles and responsibilities of the SFDA

Within 60 days from submission of the draft protocol, the SFDA shall issue a letter endorsing the draft protocol, a letter of objection or a letter notifying the MAH that the study is a clinical trial. The letter of objection shall set out in detail the grounds for the objection in any of the following cases:

- it is considered that the conduct of the study promotes the use of a medicinal product;
- it is considered that the design of the study does not fulfil the study objectives.

In case of submission of an amended study protocol, the SFDA, shall assess the amendments and inform the MAH of its endorsement or objection. The SFDA will provide the MAH with a letter of endorsement or objection to the protocol amendment within 60 days of submission. The letter of objection will provide a timeline by which the MAH should resubmit an amended version of the protocol.

VIII.C.3. Changes to the marketing authorization following results from a non-interventional PASS

The MAH shall evaluate whether the study results have an impact on the marketing authorization and shall, if necessary, submit to the SFDA to vary the marketing authorization. In such case, the variation should be submitted to the SFDA with the final study report within 12 months of the end of data collection.

Following the review of the final study report, the SFDA may recommend variation, suspension or revocation of the marketing authorization. The recommendation by the SFDA shall mention any divergent positions and the grounds on which they are based.

VIII. Appendix 1. Methods for post-authorization safety studies

VIII.App1.1. Study designs

Post-authorization safety studies may adopt different designs depending on their objectives. A brief description of the main types of studies, as well as the types of data resources available, is provided hereafter. However, this Appendix is not intended to be exhaustive and should be complemented with other information sources, such as the ENCePP Guide for Methodological Standards.

VIII.App1.1.1. Active surveillance

Active surveillance, in contrast to passive surveillance, seeks to ascertain more completely the number of adverse events in a given population via a continuous organized process. An example of active surveillance is the follow-up of patients treated with a particular medicinal product through a risk management system. Patients who fill a prescription for this product may be asked to complete a brief survey form and give permission to be contacted at a later stage. In general, it is more feasible to get comprehensive data on individual adverse event reports through an active surveillance system than through a passive reporting system. However, some of the limitations of spontaneous reporting systems still apply, especially when evaluating delayed effects. Automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings may also provide an efficient active surveillance system.

VIII.App1.1.1.1. Intensive monitoring schemes

Intensive monitoring is a system of record collation in designated areas, e.g. hospital units or by specific healthcare professionals in community practice. In such cases, the data collection may be undertaken by monitors who attend ward rounds, where they gather information concerning undesirable or unintended events thought by the attending physician to be (potentially) causally related to the medication. Monitoring may also be focused on certain major events that tend to be drug-related such as jaundice, renal failure, hematological disorders, bleeding. The major strength of such systems is that the monitors may document important information about the events and exposure to medicinal products. The major limitation is the need to maintain a trained monitoring team over time.

Intensive monitoring may be achieved by reviewing medical records or interviewing patients

and/or physicians/pharmacists in a sample of sentinel sites to ensure complete and accurate data on reported adverse events. The selected sites may provide information, such as data from specific patient subgroups that would not be available in a passive spontaneous reporting system. Further, collection of information on the use of a medicinal product, such as the potential for abuse, may be targeted at selected sentinel sites. Some of the major weaknesses of sentinel sites are problems with selection bias, small numbers of patients, and increased costs. Intensive monitoring with sentinel sites is most efficient for those medicinal products used mainly in institutional settings such as hospitals, nursing homes, and hemodialysis centers. Institutional settings may have a greater frequency of use for certain products and may provide an infrastructure for dedicated reporting. In addition, automatic detection of abnormal laboratory values from computerized laboratory reports in certain clinical settings may provide an efficient active surveillance system.

VIII.App1.1.1.2. Prescription event monitoring

In prescription event monitoring (PEM), patients may be identified from electronic prescription data or automated health insurance claims. A follow-up questionnaire can then be sent to each prescribing physician or patient at pre-specified intervals to obtain outcome information. Information on patient demographics, indication for treatment, duration of therapy (including start dates), dosage, clinical events, and reasons for discontinuation can be included in the questionnaire. PEM tends to be used as a method to study safety just after product launch and is akin to enhanced surveillance. Limitations of prescription event monitoring include substantial loss to follow-up, relatively short duration of follow-up, selective sampling, selective reporting and limited scope to study products which are used exclusively in hospitals. However, in PEM, there is the opportunity to collect more detailed information on adverse events from a large number of physicians and/or patients.

VIII.App1.1.1.3. Registries

A registry is an organized system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. A registry can be used as a data source within which studies can be performed. Entry in a registry is generally defined either by diagnosis of a disease, prescription of a medicinal product, or both (patients with a certain disease treated with a defined medicinal product, defined active substance or any medicine of a defined class of medicinal products). The choice of the registry population

and the design of the registry should be driven by its objective(s) in terms of outcomes to be measured and analyses and comparisons to be performed.

Registries are particularly useful when dealing with a rare disease, rare exposure or special population. In many cases, registries can be enriched with data on outcomes, confounding variables and effect modifiers obtained from a linkage to an existing databases.

Depending on their objective, registries may provide data on patient, disease and treatment outcomes, and of their determinants. Data on outcomes may include data on patient-reported outcomes, clinical conditions, medicines utilization patterns and safety and effectiveness. Registries should normally not be used to demonstrate efficacy of a medicinal product. Rather, once efficacy has been demonstrated in randomized clinical trials (RCTs), patient registries may be useful to study effectiveness in heterogeneous populations, effect modifiers, such as doses that have been prescribed by physicians and that may differ from those used in RCTs, patient sub-groups defined by variables such as age, co-morbidities, use of concomitant medication or genetic factors, or factors related to a defined country or healthcare system.

Where adequate data are already available or can be collected, patient registries may be used to compare risks of outcomes between different groups. For example, a case-control study may be performed to compare the exposure to the medicinal product of cases of severe adverse reactions identified from the registry and of controls selected from either patient within the registry or from outside the registry. Case-only designs may also be applied (see VIII.App 1.1.2.4.).

Patient registries may address exposure to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Simple cohort studies may measure incidence, but, without a comparison group, cannot evaluate any association between exposures and outcomes. Nonetheless, they may be useful for signal amplification particularly for rare outcomes. This type of registry may be very valuable when examining the safety of an orphan medicinal product authorized for a specific condition.

VIII.App1.1.2. Observational studies

Traditional epidemiological methods are a key component in the evaluation of adverse events. There are a number of observational study designs that are useful in validating signals from spontaneous reports, active surveillance programs or case series. Major types of these designs are

cross-sectional studies, case-control studies, and cohort studies, based on primary data collection or secondary use of existing data.

VIII.App1.1.2.1. Cross-sectional study

Data collected on a population of patients at a single point in time (or interval of time) regardless of exposure or disease status constitute a cross-sectional study. These types of studies are primarily used to gather data for surveys or for ecological analyses. A drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed, which limits its use for etiologic research unless the exposures do not change over time. These studies are best used to examine the prevalence of a disease at one time-point or to examine trends over time, when data for serial time-points can be captured. These studies may also be used to examine the crude association between exposure and outcome in ecologic analyses.

VIII.App1.1.2.2. Cohort Study

In a cohort study, a population-at-risk for an event of interest is followed over time for the occurrence of that event. Information on exposure status is known throughout the follow-up period for each patient. A patient might be exposed to a medicinal product at one time during follow-up, but non-exposed at another time point. Since the population exposure during follow-up is known, incidence rates can be calculated. In many cohort studies involving exposure to medicinal product(s), comparison cohorts of interest are selected on the basis of medication use and followed over time. Cohort studies are useful when there is a need to know the incidence rates of adverse events in addition to the relative risks of adverse events. They are also useful for the evaluation of multiple adverse events within the same study. However, it may be difficult to recruit sufficient numbers of patients who are exposed to a product of interest (such as an orphan drug) or to study very rare outcomes. The identification of patients for cohort studies may come from large automated databases or from data collected specifically for the study at hand. In addition, cohort studies may be used to examine safety concerns in special populations (the elderly, children, patients with co-morbid conditions, pregnant women) through over-sampling of these patients or by stratifying the cohort if sufficient numbers of patients exist.

VIII.App1.1.2.3. Case-control study

In a case-control study, cases of disease (or events) are identified and patients from the source

population that gave rise to the cases but who do not have the disease or event of interest at the time of selection are then selected as controls. The odds of exposure are then compared between the two groups. Patients may be identified from an existing database or using a field study approach, in which data are collected specifically for the purpose of the case control study. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (e.g. the older persons, children, pregnant women). Existing large population-based databases are a useful and efficient means of providing needed exposure and medical outcome data in a relatively short period of time. Case-control studies are particularly useful when the goal is to investigate whether there is an association between a medicinal product (or products) and one specific rare adverse event, as well as to identify multiple risk factors for adverse events. Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the exposure to the medicinal product and the adverse event. If all cases of interest (or a well-defined fraction of cases) in the catchment area are captured and the fraction of controls from the source population is known, a case-control study may also provide the absolute incidence rate of the event.

When the source population for the case-control study is a well-defined cohort, it is then possible to select a random sample from it to form the control series.

A case-control approach could also be set up as a permanent scheme to identify and quantify risks (case-control surveillance). This strategy has been followed for rare diseases with a relevant etiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders.

VIII.App1.1.2.4. Case-only designs

Case-only designs have been proposed to assess the association between intermittent exposures and short-term events, including the self-controlled case-series, the case-crossover and the case-time-control studies. In these designs, only cases are used, and the control information is obtained from past person-time experience of the cases themselves. One of the important strengths of these designs is that those confounding variables that do not change within individuals are automatically matched. However, case-only designs cannot be used under all circumstances, for instance when the exact date of disease onset is difficult to establish or when evaluating chronic exposures.

VIII.App1.1.3. Clinical trials

When important risks are identified from pre-approval clinical trials, further clinical trials might be called for to evaluate the mechanism of action for the adverse reaction. If the study is a clinical trial, national legislation of clinical trials should be followed. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing regimen can put patients at an increased risk of adverse events. Genetic testing may also provide clues about which group of patients might be at an increased risk of adverse reactions. Furthermore, based on the pharmacological properties and the expected use of the medicinal product in clinical practice, conducting specific studies to investigate potential drug-drug interactions and food-drug interactions might be called for. These studies may include population pharmacokinetic studies and therapeutic drug monitoring in patients and normal volunteers.

Sometimes, potential risks or unforeseen benefits in special populations might be identified from pre-approval clinical trials but cannot be fully quantified due to small sample sizes or the exclusion of subpopulations of patients from these clinical studies. These populations might include older persons, women of childbearing potential, children, or patients with renal or hepatic disorder. Children, the elderly, and patients with co-morbid conditions might metabolize medicinal products differently than patients typically enrolled in clinical trials. Further clinical trials might be used to determine and to quantify the magnitude of the risk (or benefit) in such populations.

VIII.App1.1.3.1. Large simple trials

A large simple trial is a specific form of clinical trial where large numbers of patients are randomized to treatment, but data collection and monitoring is kept to the minimum, consistent with the aims of the study to be a relatively low burden. This design may be used in pharmacovigilance to elucidate the benefit-risk profile of a medicinal product outside of the formal/traditional clinical trial setting and/or to fully quantify the risk of a critical but relatively rare adverse event. The use of the term ‘simple’ refers to data structure and not data collection. It is used in relation to situations in which limited information is collected regarding exposure, outcome and potential confounders to help ensure feasibility of recruiting large patient numbers in an experimental design, and the term may not adequately reflect the complexity of the studies undertaken. These studies qualify as clinical trials. As used in this context, the definitions of a pragmatic trial and of a large simple trial are synonymous.

VIII.App1.1.4. Drug utilization studies

Drug utilization studies (DUS) describe how a medicinal product is, prescribed and used in routine clinical practice in large populations, including elderly patients, children, pregnant women or patients with hepatic or renal dysfunction, who are often not eligible for inclusion in randomized clinical trials. Stratification by age, gender, concomitant medication and other characteristics allows a comprehensive characterization of treated patients, including the distribution of those factors that may influence clinical, social, and economic outcomes. From these studies, in some cases denominator data may be derived for use in determining rates of adverse events. DUS have been used to describe the effect of regulatory actions and media attention on the use of medicinal products, as well as to develop estimates of the economic burden of adverse reactions. DUS may be used to examine the relationship between recommended and actual clinical practice. These studies may help to monitor use in everyday medical practice and medication error and to determine whether a medicinal product has potential for abuse by examining whether patients are taking escalating dose regimens or whether there is evidence of inappropriate repeat prescribing. DUS are particularly useful as a first step in the design of post-authorization safety studies, to obtain sufficient understanding of the characteristics of the user population of the medicinal product under study and the determination of the most appropriate comparator as well as important potential confounders to consider.

VIII.App1.2. Data sources

Pharmacoepidemiologic studies may be performed using a variety of data sources. Traditionally, field studies were required for retrieving the necessary data on exposure, outcomes, potential confounders and other variables, through interview of appropriate subjects (e.g. patients, relatives) or by consulting the paper-based medical records. However, the advent of automated healthcare databases has remarkably increased the efficiency of pharmacoepidemiologic research. There are two main types of automated databases, those that contain comprehensive medical information, including prescriptions, diagnosis, referral letters and discharge reports, and those mainly created for administrative purposes, which require a record-linkage between pharmacy claims and medical claims databases. These datasets may include millions of patients and allow for large studies. A major limitation however often is the lack of long-term follow up and the consequent left- and right- censoring of data. In addition, these databases may not have the detailed and accurate

information needed for some research, such as validated diagnostic information or laboratory data, and paper-based medical records should be consulted to ascertain and validate test results and medical diagnoses. Depending on the outcome of interest, the validation may require either a case-by-case approach or just the review of a random sample of cases. Other key aspects may require validation where appropriate. There are many databases in place for potential use in pharmacoepidemiologic studies or in their validation phase.

MAHs should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results). External validity should also be considered. As far as feasible the data source chosen to perform the study should include the population in which the safety concern has been raised. In case another population is involved, the MAH should evaluate the differences that may exist in the relevant variables (e.g. age, sex, pattern of use of the medicinal product) and the potential impact on the results. In the statistical analysis, the potential effect of modification of such variables should be explored.

With any data source used, the privacy and confidentiality regulations that apply to personal data should be followed.

MODULE IX – SIGNAL MANAGEMENT

IX.A. INTRODUCTION

The objectives of this Module are:

- To provide general guidance and requirements on structures and processes involved in signal management (section IX.A.);
- To describe how these structures and processes are applied in the setting of the pharmacovigilance and regulatory network (section IX.B.).

Individual organisations may follow alternative signal management processes and terminology but should encompass the general principles outlined in this Module.

IX.A.1. Terminology

Signal definition

Signal is an information that arises from one or multiple, including observations or 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. For the purpose of this Module, only new information related to adverse effects will be considered.

Signal management process

Signal management process is a set of activities performed to determine whether there are new risks associated with an active substance or a medicinal product or whether known risks have changed, based on ICSRs, aggregated data from active surveillance systems or studies, literature information or other data sources

The signal management process includes the following activities from signal detection to recommendation for action (Figure 1):

- Signal detection
- Signal validation
- Signal analysis and prioritization
- Signal assessment
- Recommendation for action

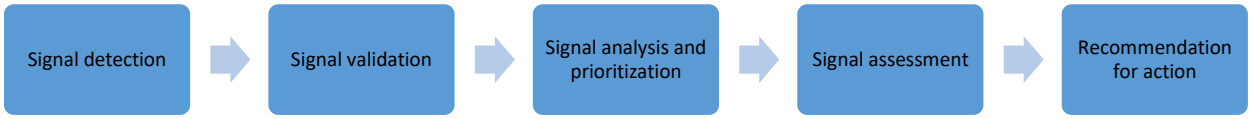


Figure 1: Signal management process

Signal validation

Signal validation is the process of evaluating the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence to demonstrate that there is a new causal association.

Validated signal

A signal for which the signal validation process has verified that the available documentation contains sufficient evidence demonstrating the existence of a new potentially causal association.

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.

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.

Refuted signal

A validated signal, which following further assessment has been, determined to be “false” i.e. a causal association cannot be established at that point in time.

Signal monitoring

When reviewing new information from ICSRs or the scientific literature at appropriate time intervals to determine whether the new data is supportive of a causal relationship.

Verified Signal

A validated signal, which following further assessment has been determined to be "true" i.e. a causal association is established at that point in time.

Emerging safety issue

A safety issue considered by a MAH to require urgent attention by the SFDA because of the potential major impact on the benefit-risk 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 special warning and precaution, contraindication, a restriction of use of a medicinal product or its withdrawal from the market;
- Major safety-related regulatory actions outside Saudi Arabia, e.g. a restriction of use of a medicinal product or its suspension.

IX.B. SIGNAL STRUCTURE AND PROCESS

IX.B.1. Sources of data and information

The sources for identifying new signals are diverse. They potentially include all scientific information concerning the use of medicinal products including quality, non-clinical, clinical (including pharmacovigilance and pharmacoepidemiological data).

Specific sources for signal detections include:

- Spontaneous ADR reporting systems.
- Active surveillance systems.
- Scientific literature including observational studies, clinical trials, meta analyses.

Signals from spontaneous reports may be detected from:

- Monitoring of ICSRs, ADR databases, articles from the scientific literature.
- Information provided by MAHs in the context of regulatory procedures (e.g. variations, renewals, post-authorization commitments, PSUR/PBRERs, or RMP updates.
- From other activities related to the on-going benefit-risk monitoring of medicinal products.

IX.B.2. Signal detection

Signal detection should be based on a multidisciplinary approach following recognized methodology, which may vary depending on the type of medicinal product it is intended to cover.

Signal detection may be performed based on a review of ICSRs, statistical analyses, or from a combination of both, depending on the size of the data set.

IX.B.3. Signal validation

Signal validation should consider the clinical relevance including:

- Strength of evidence for a causal effect, e.g.:
  - Number of cases (after exclusion of duplicates);
  - Patient's demographics (including age and gender);
  - Suspected medicinal product (including dose administered, formulation);
  - Suspected adverse reaction (including signs and symptoms);
  - Clinical outcome in relation to drug continuation or discontinuation (i.e. de-challenge / re-challenge information);
  - Assessment of temporal and causality of association;
  - Potential confounders (including other concomitant medications, the underlying disease, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship);
  - Seriousness and severity of the reaction and its outcome;

- Novelty of the reaction (e.g. new and serious adverse reactions);
- Drug-drug interactions;
- Reactions occurring in special populations.

- Previous awareness, e.g.:
  - The extent to which information is already included in the SPC or PIL
  - The association has already been assessed in a PSUR/PBRER or RMP
  - The information was discussed at the level of a scientific committee or has been subject to a regulatory procedure
- Availability of other relevant sources of information providing a richer set of data on the same association
  - Literature findings regarding similar cases;
  - Experimental findings or biological mechanisms;
  - Screening of databases with larger datasets.
- Additional sources of information may provide further evidence on the association. For example:
  - Databases with larger datasets, when the signal was detected from national or company-specific databases;
  - Healthcare databases that may provide information on characteristics of exposed patients and medicines utilization patterns,
  - Information from other regulatory authorities.

The evaluation of the evidence supporting a signal may involve several rounds of expert discussions and different levels of decision-making. This may result in various decisions; closing or monitoring signal.

IX.B.4. Signal analysis and prioritization

A key element of the signal management process is to promptly identify validated signals with important public health impact or that may significantly affect the benefit-risk profile of the medicinal product.

This prioritization process should consider the following:

- Severity, seriousness, and reversibility of the adverse reaction;

- The consequences of treatment discontinuation and the availability of other therapeutic options;
- The strength and consistency of the evidence supporting an association;
- Clinical context (e.g. whether the association suggest a clinical syndrome that may include other reactions);
- The public health impact includes;
  - The extent of utilization of the product in the general population and in special populations (e.g. pregnant women, children or elderly)
  - The patterns of medicinal product utilization (e.g. off-label use or misuse)
  - Estimation of the number of patients that may be affected by an adverse reaction
- Novelty of the suspected adverse reaction, e.g. when an unknown suspected adverse reaction occurs shortly after the marketing of a new medicinal product;
- If the new active substance application of MAHs is still under evaluation.

In some circumstances, priority may also be given to signals with high potential media and/or public concern. The outcome of signal prioritization should include timeline for the management of the signal.

IX.B.5. Signal assessment

The objective of signal assessment is to further evaluate a validated signal to identify the need for additional data collection or for any regulatory action. This review should consist of product indication, literature articles, spontaneous reports, expert consultation, and information held by other regulators and MAHs when available. The strengths and limitations of each source should be considered in order to assess the contribution to overall evaluation of the signal in terms of a recommendation for action.

Signal assessment should be extended as needed to include the followings:

- Adverse reaction at broader level e.g. at the therapeutic or system organ class level or at the level of a Standardized MedDRA Query (i.e. SMQ);
- Other adverse reactions, such as to other terms linked to a complex disease (e.g. optic neuritis as a possible early sign of multiple sclerosis);
- Other products of the class;

- Prior stage of a reaction (e.g. QT prolongation and torsades de pointes);
- Clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure).

IX.B.6. Recommendation for action

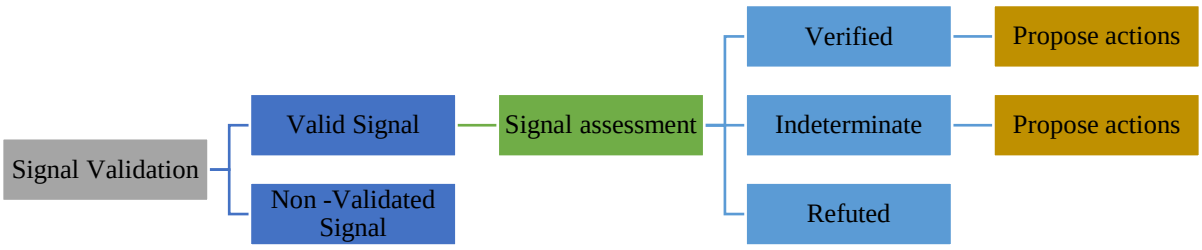


Figure 2**: Signal evaluation process**

The following are some of the recommended actions:

- Additional risk minimization measures or immediate measures includes suspending the medicinal product
- Additional information to be provided by the MAH, e.g. in order to confirm if a conclusion is valid for all indications and patient groups
- Periodic review of the signal through PSUR/PBRERs (Module VII)
- Update of the product information through a regulatory procedure (SPC and PIL). The MAH should send a notification of variation submission for the SPC/PIL update through email (NPC.Drug@sfda.gov.sa).
- Conduct a PASS (Module VIII)

Whenever actions are requested from MAH, the request should specify a timeframe by which they should be completed.

IX.B.7. Statistical analyses

Signal detection is increasingly based on a regular periodic monitoring of large databases of spontaneous reports of ADRs. Such databases allow generation of statistical reports presenting

information on adverse reactions received over a defined time period for certain active substances or medicinal products. Various statistical methods have been developed to identify disproportionate reporting, i.e. higher reporting than expected for a suspected adverse reaction for an active substance/medicinal product of interest compared to all other active substances/medicinal products in the database, (e.g. as a lower bound of the proportionate reporting ratio (PRR) >1). Statistics of disproportionate reporting alone do not necessarily indicate that there is a signal to be further investigated or that a causal association is present.

The following should be considered when using statistical methods and the selection of criteria for the detection of signals:

- The size of the data set
- The completeness of the available information and the severity of the adverse reaction(s)

Statistical reports may be designed to provide tools for identifying suspected adverse reactions that meet pre-defined criteria of frequency, severity, clinical importance, novelty or statistical association. Such filtering tools may facilitate the selection of ICSRs to be reviewed as a first step. The thresholds used in this filtering process (for example, at least 3 cases reported) may vary according to the extent of usage of medicinal products and thus the potential public health impact.

Irrespective of the statistical method used, where statistical reports are used to automate the screening of a database, signal detection should always involve clinical judgement and the corresponding ICSRs should be individually reviewed, considering their clinical relevance.

The statistical method should therefore be a supporting tool in the whole process of signal detection and subsequent validation.

IX.B.8. Quality requirements

Signal management is considered a critical process (Module I). Any signal management system should be clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are clear and standardized, that these tasks are conducted by staff with appropriate qualifications and expertise and that there are provisions for appropriate control and, when needed, improvement of the system. A system of quality management (Module

I) should be applied to all signal management processes. Detailed procedures for this quality system should be developed, documented and implemented. This includes the rationale for the method and periodicity of signal detection activities.

Through a tracking system, all organizations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions and rationale.

The organizational roles and responsibilities for the activities including maintenance of documentation, quality control and review, and for ensuring corrective and preventive action should be assigned and recorded. Each organization should ensure that staff members are specifically trained in signal management activities in accordance with their roles and responsibilities (see GVP Module I).

MAHs should include the description of the signal management process in the pharmacovigilance system master file (Module II). The performance of the system should be controlled and, when used, performance indicators should be presented in the annex to the pharmacovigilance system master file (Module II). MAHs shall put in place a record management system for all documents used for pharmacovigilance activities that ensures the retrievability of those documents as well as the traceability of the measures taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process. As for any critical process, signal management activities should be audited at regular intervals, including tasks performed by any service providers and contractors (Module IV). Data and document confidentiality (per the applicable laws and regulations), security and validity (including data integrity when transferred between organizations) should be guaranteed.

Documentation demonstrating compliance with these requirements should be available at any time, including justification/evidence for the steps taken and decisions made.

IX.C. OPERATION WITHIN THE KSA

IX.C.1. Roles and responsibilities of MAH

It is vitally important for the MAH to monitor the safety of its products licensed in Saudi Arabia.

The following list should apply for all licensed pharmaceutical products:

1. The MAH should continuously monitor the safety of its medicinal products and inform the SFDA of any changes that might have a significant impact on the marketing authorization status.
2. The MAH should scan all information sources (MAH database, literature, international authorities, SFDA website and others) to detect any possible signal or any new evidence affecting the benefit/risk balance of the drug.
3. The local QPPV should be aware and involved in signal process related to registered product.
4. All MAHs should have systems and methods for systematic signal detection and the frequency of the monitoring should be done at least once monthly.
5. All MAHs should have official written procedural documents identifying and describing the signaling method used, such as the standard working method. These documents should provide detailed information about the roles and responsibilities of all staff involved in signal detection, the information sources involved in the analysis, and the method used for signal detection. The PSMF should also have written procedures for signal generation, detection and evaluation.
6. The MAH must adequately document the signal detection activities, including decisions and conclusions taken during these activities.
7. The MAH should monitor and take the necessary regulatory actions that published periodically by the international competent authorities such as SPC/PIL safety update after the approval of the reference country.
8. The MAH shall exchange with SFDA the assessed signals (verified, indeterminate and refuted).
9. Procedures for signal analysis should be arranged to include at least the following aspects:
   9.1. Increase in frequency, severity, or mortality rate of adverse reaction reports. The MAH must inform the NPC via email (npc.drug@sfda.gov.sa) immediately in the cases mentioned above. In addition, against the likelihood of it being a condition originating from the nature of the drug, review which processes have any change in the production of the drug, follow up the changed processes closely, make the necessary analyses and notify the NPC on the conclusion.
   9.2. Taking the necessary actions in line with the suggestions received from regulatory authority/health authority that is mentioned in the World Health Organization Listed

Authority (WHO-WLAs) and have the vigilance function listed. The list is available in WHO website "List of WHO Listed Authorities WLAs"

9.2.1. If the proposal requires any addition to SPC/PIL, the MAH of the original drug should apply to the SFDA for a variation according to section IX.C.3 and notify the NPC via email (npc.drug@sfda.gov.sa) within 21 calendar days of submitting the variation to the reference country.

10. If any international regulatory authority not mentioned in WHO-WLAs, requested safety changes such as SPC/PIL update, the QPPV shall submit the MAH signal assessment report and cover letter to NPC via email (npc.drug@sfda.gov.sa) within 180 calendar days of that request in the reference country.

11. For any valid signal arising from the MAH database, the MAH:
    a) Shall assess the signal and submit a signal assessment report to the NPC via email (npc.drug@sfda.gov.sa) within 180 calendar days of detection.
    b) The report should contain all information available at that point including but not limited to (signal assessment report, clinical or epidemiological studies, ICSR, pharmacological plausibility, etc.).
    c) All-new available or follow-up information (which has an impact on public health or has an impact on the benefit-risk balance of the product) raised after submitting the signal should be sent to SFDA within 15 calendar days.
    d) Should collaborate with the SFDA to provide additional information upon request.
    e) For verified signal, MAH should communicate the proposed action plan including the submission of a variation request regarding the signal.
    f) If the action plan requires any addition to SPC/PIL, MAH should attach with the signal assessment report the proposed text that will be added it to the SPC/PIL.

12. If requested by SFDA, the MAH shall provide an assessment report for signals within 90 calendar days starting from the requested date. The assessment report must include, but not limited to:

    a. Results from clinical trials database, epidemiology, preclinical findings, Post-Authorization Safety Study, global pharmacovigilance database and medical literature

    b. Possible pharmacological mechanism of the ADR.

    c. The potential impact on the therapeutic plan if there is a discontinuation of the product due to (risk x) as adverse drug event.

d. Conclusion

e. If there is any proposed risk minimization measure.

13. The MAH should keep an audit trail of its signal detection activities.
14. All submitted signals should be accompanied by filled signal cover letter templet can be found in annex IX Appendix I.

IX. C.2 Emerging safety issues

1. The MAH should notify in writing as an Emerging Safety Issue to the SFDA in writing and through NPC email (npc.drug@sfda.gov.sa) if any safety issue arises from its signal detection activities that could have a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health. The notification shall be done within 7 calendar days.
2. When notifying an emerging safety issue, 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 SFDA as soon as it becomes available.
3. The MAH should only communicate as emerging safety issues those safety concerns that meet the definition provided in IX.A.1, i.e., those that meet the urgency and seriousness cannot permit any delay in handling.
4. New safety information related to quality defects or suspected falsified medicinal products which might influence the evaluation of the benefits and risks of the medicinal product and which may give rise to an abnormal restriction in supply should not be notified as an emerging safety issue.

IX.C.3 Variation of the terms of marketing authorization

A MAH may conclude, based on their assessment of a signal detected through the monitoring data that the product information should be updated through a variation. In such cases, the MAH should submit the approved action plan as a variation application to the SFDA as soon as possible upon next available variation in accordance to variation guideline

MAHs should follow the relevant guidance on variations, including work-sharing procedures, as appropriate when preparing their variation application.

IX Appendix I

Cover Letter Information

Please note: the cover letter of reported signal should include but not limited to the following information.

Signal General information		
Name of the Active Ingredient		
Drug International Birthdate		
Saudi Registration Status (Registered – Under registration– Not registered)		
Name of the Adverse Event		
Source of the Signal		
Date of Signal Detection		
Date of Submission*		
Signal Outcome based on final assessment report (verified – Refuted – Under evaluation*)		
Summary of Signal Assessment Report		
	Yes	**No**
Number of Cases (>3 cases)		
Local Cases		
Serious Health Consequence**		
Valid Biological Plausibility of ADR		
Verified Signal (Confirmed Risk)		
Based on the Signal, Will **Saudi** Label be Updated ? (If yes, specify which section)		
➢ Contraindication		
➢ Warning and Precaution or Black Box Warning		
➢ Undesirable Events		
Additional Risk Minimization Measures Based on the Signal (please specify) ……		

*Signal full assessment report should be submitted within 180 calendar days from detection.

**Signal considered serious if the worst known outcome was one of the following: Fatality (more that 1% of the cases), disability or major transient sequel.

MODULE X – ADDITIONAL MONITORING

X.A. Introduction

Pharmacovigilance is a vital public health function with the aim of rapidly detecting and responding to potential safety hazards associated with the use of medicinal products.

A medicinal product is authorized on the basis that, its benefit-risk balance is considered to be positive at that time for a specified target population within its approved indication(s). However, not all risks can be identified at the time of initial authorization and some of the risks associated with the use of a medicinal product emerge or are further characterized in the post-authorization phase of the product's lifecycle. To strengthen the safety monitoring of medicinal products, , a framework for enhanced risk proportionate post-authorization data collection for medicinal products has been introduced, including the concept of additional monitoring for certain medicinal products.

The SFDA shall set up, maintain and make public a list of medicinal products that are subject to additional monitoring (hereafter referred to as "the list"). These medicinal products will be readily identifiable by an inverted equilateral black triangle. That triangle will be followed by an explanatory statement in the SPC as follows:

"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 to the NPC in Saudi Arabia. Reporting information is provided in "report any side effects" section.

A similar statement will also be included in the package leaflet. This explanatory statement should encourage healthcare professionals and patients to report all suspected adverse reactions.

This GVP takes into account the new provisions relating to the list of products which require additional monitoring.

Post-authorization spontaneous reports remain a cornerstone of pharmacovigilance. Data from spontaneous reports is a key source of information for signal detection activities (see Module IX). Increasing the awareness of healthcare professionals and patients of the need to report suspected ADRs and encouraging their reporting is therefore an important means of monitoring the safety profile of a medicinal product.

The concept of additional monitoring originates primarily from the need to enhance the ADR

reporting rates for newly authorized products for which the safety profile might not be fully characterized or for products with newly emerging safety concerns that also need to be better characterized. The main goals are to collect additional information as early as possible to further elucidate the risk profile of products when used in clinical practice and thereby informing the safe and effective use of medicinal products.

X.B. STRUCTURES AND PROCESSES

X.B.1. Principles for assigning additional monitoring status to a medicinal product

All medicines are authorized on the basis that the benefit of treatment is considered to outweigh the potential risks. To come to this conclusion for a marketing authorization, data from clinical trials conducted during the development of a medicine are assessed. However, adverse reactions which occur rarely or after a long time may become apparent only once the product is used in a wider population and/or after long term use. In addition, the benefits and risks of a medicine may have been evaluated in conditions which may differ from those in everyday medical practice, e.g. clinical trials might exclude certain types of patients with multiple co-morbidities or concomitant medications. Therefore, after a medicine is placed on the market, its use in the wider population requires continuous monitoring. MAH and the SFDA continuously monitor medicinal products for any information that becomes available and assess whether it impacts on the benefit-risk profile of the medicinal product. However, for certain medicinal products enhanced post authorization data collection is needed to ensure that any new safety hazards are identified as promptly as possible and that appropriate action can be initiated immediately. Therefore, in order to strengthen the monitoring of certain medicinal products and in particular to encourage the spontaneous reporting of ADRs, the concept of additional monitoring has been introduced.

Additional monitoring status can be assigned to a medicinal product at the time of granting a marketing authorization or in some cases at later stages of the product life cycle for a medicinal product for which a new safety concern has been identified. The additional monitoring status is particularly important when granting marketing authorization for medicinal products containing a new active substance and for all biological medicinal products, which are priorities for pharmacovigilance. The SFDA may also require additional monitoring status for a medicinal

product which is subject to specific obligations e.g. the conduct of a PASS or restrictions with regards to the safe and effective use of the medicinal product.

X.B.2. Communication and transparency

The additional monitoring status needs to be communicated to healthcare professionals and patients in such a way that it increases reporting of suspected adverse reactions without creating undue alarm. This can be achieved for example by highlighting the need to better characterize the safety profile of a new medicinal product by identifying additional risks but placing those potential risks in the context of the known benefits for this product. A publicly available list of medicinal products with additional monitoring status should be kept up to date by the SFDA. In addition, healthcare professionals and patients should be enabled to easily identify those products through their product labelling. The publication of the list together with appropriate communication should encourage healthcare professionals and patients to report all suspected ADRs for all medicinal products subject to additional monitoring.

X.C. OPERATION WITHIN THE KSA

X.C.1. Criteria for including a medicinal product in the additional monitoring list

It is mandatory to include the following categories of medicinal products in the additional monitoring list:

- Medicinal product authorized in Saudi Arabia that contains a new chemical entity.
- Biological medicinal products.
- Biosimilar medicinal products.
- Products for which a PASS was requested at the time of marketing authorization.
- Products for which a PASS was requested following the grant of marketing authorization.
- Registered products that have been granted an approval for a new indication based on phase 2 trials.
- Other medicinal product upon SFDA request.

Pharmacovigilance rules in general and additional monitoring specifically take into account that

the full safety profile of medicinal products can only be confirmed after products have been placed on the market. Due consideration should, therefore, be given to the merit of inclusion of a medicinal product in the list in terms of increasing awareness about the safe and effective use of a medicinal product and/or providing any additional information for the evaluation of the product. In this regard, the decision to include a medicinal product subject to conditions in the list should take account of the nature and scope of the conditions or obligations placed on the marketing authorization including their potential public health impact. The decision should also consider the usefulness of the additional monitoring status in relation to other additional pharmacovigilance activities proposed in the RMP, for example in relation to the objectives of PASS.

The initial period of inclusion in the additional monitoring list is five years.

X.C.2. Roles and responsibilities

X.C.2.1. The SFDA

- Is responsible for publishing a list of medicinal products that are subject to additional monitoring on the SFDA website;
- Is responsible for removing medicinal products from the list after a pre-determined period;
- Will take into account the list of medicinal products subject to additional monitoring in determining the frequency and processes of its signal detection activities;
- Will inform the relevant MAH when a medicinal product has been included to the list of additional monitored products.

X.C.2.2. The marketing authorization holder

The MAH:

- Shall include in the SPC and Package leaflet of their medicinal products subject to additional monitoring the black triangle symbol and the standardized explanatory statement on additional monitoring;
- Should include information on the status of additional monitoring in any material to be distributed to healthcare professionals and patients and should make all efforts to encourage reporting of adverse reactions, as agreed with the SFDA;

- Should submit the relevant variation to include/remove the black symbol, the statement, and the standardized explanatory sentence from the SPC and PL, where applicable.

X.C.3. Creation and maintenance of the list

The SFDA shall set up, maintain and make public a list of medicinal products that are subject to additional monitoring. This list will include the names and active substances of all medicinal products approved in the KSA subject to additional monitoring.

X.C.3.1. Process for the creation of the list

The SFDA will identify the authorized products requiring additional monitoring.
The SFDA will maintain the information that is publicly available and ensure that it is up to date.
The SFDA will make the list available to the public.

X.C.3.2. Process for the maintenance of the list

The list will be updated quarterly, as appropriate.

X.C.4. Black symbol and explanatory statements

For medicinal products included in the list, the SPC shall include the 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 to the NPC in Saudi Arabia. Reporting information is provided in “report any side effects” section.
This statement should be preceded by an inverted equilateral black triangle. A similar statement will also be included in the package leaflet. Once the medicinal product is included or removed from the list, the MAH shall update the SPC and the package leaflet to include or remove, as appropriate, the black symbol, the statement, and the standardized explanatory statement.
If the decision to include or remove a medicinal product from the list is done during the assessment of a regulatory procedure (e.g. marketing authorization application, extension of indication, renewal) the SPC and the package leaflet should be updated before finalization of the procedure in order to include or remove the black triangle symbol and explanatory statement from the product information.

X.C.5. Transparency

The SFDA will make publicly available the list of the names and active substances of all medicinal products approved in the KSA subject to additional monitoring and the general criteria to include medicinal products in the list.

MODULE XV – SAFETY COMMUNICATION

XV.A. INTRODUCTION

This Module provides guidance to MAHs and the SFDA on how to communicate and coordinate safety information in the KSA. 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 and contributing to the protection of patients' and public health (see Module I).

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 SPC, PIL and the labelling of the packaging) and public assessment reports. Although some principles in this Module (i.e. Section XV.B.1 and B.2.) apply to all types of safety communication, the module itself focuses on the communication of 'new or emerging safety information', which means new information about a previously known or unknown risk of a medicine which has or may have an impact on a medicine's benefit-risk balance and its condition of use. Unless otherwise stated, the term 'safety communication' in this module should be read as referring to emerging safety information.

Communication of important new safety information on medicinal products should consider the views and expectations of concerned parties, including patients and healthcare professionals, with due consideration given to relevant legislation. This Module addresses some aspects of the interaction with concerned parties and supplements the specific guidance given in Module XI on public participation.

Communication is distinct from transparency, which aims to provide public access to information related to data assessment, decision-making and safety monitoring performed by the SFDA.

Section XV.B. of this Module describes principles, means of safety communication, dissemination

of safety communications and guidance on the coordination. This section provides particular consideration to direct healthcare professional communications (DHPCs) and provide specific guidance for preparing them. This is because of the importance of DHPCs in targeting healthcare professionals and because of the level of coordination required between MAHs and the SFDA in their preparation.

XV.B. STRUCTURES AND PROCESSES

XV.B.1. Objectives of safety communication

Safety communication aims to:

- Provide timely, evidence-based information on the safe and effective use of medicines;
- Facilitating changes to healthcare practices (including self-medication practices) where necessary;
- Change attitudes, decisions and behaviors in relation to the use of medicines;
- Support risk minimization behavior;
- Facilitate 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.

XV.B.2. Principles of safety communication

The following principles of safety communication should be applied:

- The need for communicating safety information should be considered throughout the pharmacovigilance and risk management process and should be part of risk assessment.
- There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. the SFDA, other public bodies and MAHs).
- Safety communication should deliver relevant, clear, accurate and consistent messages and reach the right audiences at the right time for them to take appropriate action.
- Safety communication should be tailored to the appropriate audiences (e.g. patients and healthcare professionals) by using appropriate language and taking account of the different levels of knowledge and information needs whilst maintaining the accuracy and consistency of the information conveyed.

- Information on risks should be presented in the context of the benefits of the medicine and include available and relevant information on the seriousness, severity, frequency, risk factors, time to onset, reversibility of potential adverse reactions and, if available, expected time to recovery.
- Safety communication should address the uncertainties related to a safety concern. This is of particular relevance for emerging information which is often communicated while the SFDA are conducting their evaluations; the usefulness of communication at this stage needs to be balanced against the potential for confusion if uncertainties are not properly represented.
- Information on competing risks such as the risk of non-treatment should be included where appropriate.
- The most appropriate quantitative measures should be used when describing and comparing risks, e.g. the use of absolute risks and not just relative risks; for risk comparisons, denominators should be the same in size. The use of other tools such as graphical presentation of the risk and/or the benefit-risk balance may also be used.
- Patients and healthcare professionals should, where possible, be consulted and messages pre-tested early in the preparation of safety communication, particularly on complex safety concerns (see Module XII, which will be realized).
- Where relevant safety communication should be complemented at a later stage with follow-up communication e.g. on the resolution of a safety concern or updated recommendations.
- The effectiveness of safety communication should be evaluated where appropriate and possible (see XV.B.7.).
- Safety communications should comply with relevant requirements relating to individual data protection and confidentiality.

XV.B.3. Target audiences

The primary target audiences for safety communication issued by regulatory authorities and MAHs should be patients and healthcare professionals who use (i.e. prescribe, handle, dispense, administer or take) medicinal products.

As primary target audiences, healthcare professionals play an essential role. Effective safety communication enables them to give clear and useful information to their patients, thereby promoting patient safety and confidence in the regulatory system. Both healthcare professionals in

clinical practice and those involved in clinical trials should be provided with appropriate information on any safety concern at the same time.

Patient, consumer and healthcare professional organizations can play a role as multipliers as they can disseminate important safety information to target audiences.

The media is also a target audience for safety communication. The capacity of the media to reach out to patients, healthcare professionals and the general public is a critical element for amplifying new and important information on medicines. The way safety information is communicated through the media will influence the public perception and it is therefore important that the media receives safety information directly from the SFDA in addition to the information they receive from other sources, such as from the MAHs.

XV.B.4. Content of safety communication

Considering the principles in XV.B.2., safety communication should contain:

- Important emerging information on any authorized medicinal product which has an impact on the medicine's benefit-risk balance under any conditions of use;
- The reason for initiating safety communication clearly explained to the target audience;
- Any recommendations to healthcare professionals and patients on how to deal with a safety concern;
- When applicable, a statement on the agreement between the MAH and the SFDA on the safety information provided;
- Information on any proposed change to the product information (e.g. SPC or PIL);
- a list of literature references, when relevant or a reference to where more detailed information can be found;
- Where relevant, a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.

The information in the safety communication shall not be misleading and shall be presented objectively. Safety information should not include any material or statement which might constitute advertising of any products.

XV.B.5. Means of safety communication

Communication tools and channels have become more numerous and varied over time, offering

the public more information than was previously possible. The use of this increasing variety of means should be considered when issuing safety communication in order to reach the target audiences and meet their growing expectations. Different communication tools and channels are discussed below in sections XV.B.5.1.-XV.B.5.9.

XV.B.5.1. Direct healthcare professional communication (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 MAH or the SFDA, 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 MAH and the SFDA. Agreement between these two parties should be reached before a DHPC is issued by the MAH. The agreement will cover both the content of the information (see XV.B.4.) and the communication plan, including the intended recipients and the timetable for disseminating the DHPC (see Module XII, which will be realized).

Where there are several marketing authorization holders of the same active substance and/or a class of products for which a DHPC is to be issued, a single consistent message should be delivered (see XV.C.2.1.).

Whenever possible, it is advised that healthcare professionals' organizations or learned societies are involved as appropriate during the preparation of DHPCs to ensure that the information they deliver is useful and adapted to the target audience.

A DHPC may be complemented by other communication tools and channels and the principle of providing consistent information should apply (XV.B.2.).

A DHPC may be an additional risk minimization measure as part of an RMP (see Modules V and XV).

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:

- New major warnings or precautions for use in the product information;
- New data identifying a previously unknown risk or a change in the frequency or severity of a known risk;
- Substantiated knowledge that the medicinal product is not as effective as previously considered;
- New recommendations for preventing or treating adverse reactions or to avoid misuse or medication error with the medicinal product;
- Ongoing assessment of an important potential risk, for which data available at a particular point in time are insufficient to take regulatory action (in this case, the DHPC 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).

The SFDA may disseminate or request the MAH to disseminate a DHPC in any situation where the SFDA considers it necessary for the continued safe and effective use of a medicinal product.

XV.B.5.2. Documents in lay language

Communication material in lay language (e.g. using a questions & answers format) helps patients and the general public to understand the scientific evidence and regulatory actions relating to a safety concern. Lay language documents should contain the SFDA recommendations and advice for risk minimization for patients and healthcare professionals in relation to the safety concern and should be accompanied by relevant background information.

Lay language documents are generally useful to members of the public who have an interest in the subject but do not have a scientific or regulatory background. Reference should be made to other communication materials on the topic to direct readers to where they can find further information.

The SFDA may publish lay language (Arabic or English) documents on the SFDA web-portals and may additionally disseminate them to relevant parties such as patients and healthcare

professionals' organizations.

Whenever possible, it is advised that patients and healthcare professionals are involved during the preparation of lay language documents to ensure that the information they deliver is useful and adapted to the target audience.

XV.B.5.3. Press communication

Press communication includes press releases and press briefings which are primarily intended for journalists.

The SFDA may send press releases directly to journalists in addition to publishing them on the websites. This ensures that journalists, in addition to obtaining information from other sources, receive information that is consistent with the authority's scientific assessment. Interaction with the media is an important way to reach out to a wider audience as well as to build trust in the regulatory system.

Press releases may also be prepared and published by MAHs. Their press releases may reflect the position of the MAH on a safety topic but should also refer to any regulatory action taken by the SFDA. Relevant ongoing reviews should be mentioned in any communication by the MAH.

Although aimed at journalists, press releases will be read by other audiences such as healthcare professionals, patients and the general public. Reference should therefore be made to related communication materials on the topic. In cases where a DHPC is also prepared, healthcare professionals should ideally receive it prior to or around the same time of the publication or distribution of a press release so that they are better prepared to respond to patients.

Press briefings with journalists should be considered by the SFDA for safety concerns or other matters relating to the safety of medicinal products that are of high media interest or when complex or public-health-sensitive messages need to be conveyed.

XV.B.5.4. Website

A website is a key tool for members of the public (including patients and healthcare professionals) actively searching the internet for specific information on medicinal products. The SFDA as well as MAHs should ensure that important safety information published on websites under their control is easily accessible and understandable by the public. Information on websites should be kept up-to-date, with any information that is out-of-date marked as such or removed.

XV.B.5.5. Other web-based communications

Online safety information may also be disseminated via other web tools. When using newer, more rapid communication channels, special attention should be paid to ensure that the accuracy of the information released is not compromised. Communication practices should consider emerging communication tools used by the various target audiences.

XV.B.5.6. Bulletins and newsletters

Bulletins and newsletters provide at regular intervals new information about medicines and their safety and effectiveness. The SFDA can reach a large audience with these tools by using web-based and other available means.

XV.B.5.7. Responding to enquiries from the public

The SFDA and MAHs should have systems in place for responding to enquiries about medicines from individual members of the public. Responses should consider the information which is in the public domain and should include the relevant recommendations to patients and healthcare professionals issued by the SFDA. Where questions relate to individual treatment advice, the patient should be advised to contact a healthcare professional.

XV.B.5.8. Other means of communication

In addition to those discussed above, there are other tools and channels such as publications in scientific journals and journals of professional bodies.

Some tools and channels may be used in the context of risk management; risk minimization measures often include specific programs for risk communication. Tools used in such programs, such as patient alert cards or healthcare professional safety guidance, are outside the scope of this module and are described in more detail in Module XVI.

XV.B.6. Effectiveness of safety communication

Safety communication is considered effective when the message transmitted is received and understood by the target audience in the way it was intended, and appropriate action is taken by the target audience. Adequate mechanisms should be introduced in order to measure the effectiveness of the communication based on clear objectives. Measuring effectiveness allows lessons to be learned and helps in making decisions on prioritizing and adapting tools and practices

to meet the needs of the target audiences. A research-based approach will normally be appropriate in order to establish that safety communications have met the standard of XV.B.2. This approach may measure different outcomes, including behavior, attitudes, and knowledge. When evaluating the effectiveness of safety communication, the scope of the evaluation may be broadened to include factors other than the performance of the individual tools used in the safety communication (see Module XVI).

In the case of DHPCs, the MAH should be responsible for evaluating the dissemination of the DHPCs they prepare and should inform the SFDA of the outcome and of any difficulties identified (e.g. problems related to the list of recipients or the timing and mechanism of dissemination). Appropriate action should be taken as needed to correct the situation or prevent similar problems in the future.

XV.B.7. Quality system requirements for safety communication

In accordance with the quality system requirements in Module I, procedures should be in place to ensure that safety communications comply with the principles in XV.B.2. as appropriate.

In particular, the communications should be subject to quality controls to ensure their accuracy and clarity. For this purpose, review procedures with allocated responsibilities should be followed and documented.

XV.C. OPERATION WITHIN THE KSA

XV.C. COORDINATION OF SAFETY ANNOUNCEMENT

XV.C.1. Requirements for the MAH

As soon as a MAH in the KSA intends to make a public announcement relating to information on pharmacovigilance concerns in relation to the use of a medicinal product, and in any event at the same time or before the public announcement is made, the MAH shall be required to inform the SFDA.

XV.C.1.2. Consideration for third parties

Third parties (e.g. scientific journals, learned societies, patients' organizations) are encouraged to inform the SFDA of any relevant emerging information on the safety of medicines authorized in the KSA and, if publication is planned, to share the information ahead of publication.

There are situations where emerging safety information is to be published or has been published by a party other than the SFDA (e.g. scientific journals, learned societies). The SFDA should bring to the attention any such safety information that they become aware of, together with the timing of the publication if known. Where necessary and after evaluation of the information, the SFDA should prepare and disseminate a lines-to-take document safety announcement to address the information from the third party.

The MAH shall ensure that information to the public is presented objectively and is not misleading. Whenever a MAH becomes aware that a third party (e.g. scientific journals, learned societies, patients' organizations, professional societies) intends to issue communication that could potentially impact the benefit-risk balance of a medicinal product authorized in the KSA, the MAH should inform the SFDA and make every effort to share the content of the communications.

XV.C.2. Direct healthcare professional communications

In the KSA, a direct healthcare professional communication (DHPC) (see XV.B.5.1.) is usually disseminated by one or a group of MAHs for the respective medicinal product(s) or active substance(s), either at the request of the SFDA, or on the MAH's own initiative. The MAH should seek the approval of the SFDA regarding the content of a DHPC (and communication plan) prior to dissemination.

XV.C.2.1. Processing of DHPCs

The situations when a DHPC is necessary or should be considered are provided in XV.B.5.1. When drafting a DHPC, the template (see Annex II) and the guidance provided in the annotations in the template should be followed as appropriate.

Prior to the distribution of DHPCs, the MAH should submit the following to the SFDA to be reviewed:

- **Draft of the proposed DHPC**;
- **Distribution plan filled in a standardized form**:
  - **Timetable for disseminating the DHPC:** Prior to the distribution of any additional risk minimization measures, including DHPCs, a standardized form must filled to describe the distribution plan and it should be submitted for review and approval by the SFDA. The proposed timetable should be appropriate according to the urgency of the safety concern (usually maximum of 60 calendar days is considered appropriate);
  - **The dissemination list:** the intended recipients HCPs groups may be general practitioners, specialists, pharmacists, nurses; hospitals/ambulatory care/other institutions as appropriate. The list should specify the intended recipients name, specialty and geographical distribution; When defining the target groups of recipients, it should be recognized that it is not only important to communicate with those HCPs who will be able or likely to prescribe or administer the medicinal product, but also to those who may diagnose adverse reactions, e.g. emergency units, poison centers, or to appropriate specialists, e.g. cardiologists. It is also important to consider provision of DHPCs to relevant pharmacists (hospital and /or community) who serve as information providers within healthcare systems and provide assistance and information to Patients, HCPs, including hospital wards and poison centers, as well as the general public.
  - **The dissemination mechanism:** how the DHPC is planned to be disseminated, the proposed mechanism should be selected appropriately to meet the dissemination timetable.

The last 3 items above are known as the communication plan and it shall be prepared according to the SFDA regulations

Once the content of a DHPC and communication plan from the MAH are agreed by the SFDA, the MAH can start dissemination of the agreed DHPC (i.e. the MAH shall NOT start disseminating the DHPC prior to obtaining the approval from the SFDA). The MAH is obligated to complete the distribution of Direct Healthcare Professional Communication (DHPC) letters within 60 days of its approval by the SFDA. In certain situations, in which information must be distributed in a timely manner, the SFDA could demand for a faster distribution that should be completed within 30 days. After dissemination of a DHPC, an evidence of the distribution process of Direct Healthcare Professional Communication (DHPC) letters must be submitted after the completion of the distribution using the standardized form.

The MAH should adhere to the Communication Plan agreed with the SFDA. Any significant event or problem occurring during the DHPC dissemination which reveals a need to change the Communication Plan or a need for further communication to Healthcare Professionals, this should be notified in a timely manner to the SFDA to be approved.

In cases where a medicines authority in other country requests the dissemination of a DHPC in its territory, the MAH should notify the SFDA if this product is also authorized. This is in the context of the national legal requirement under which the MAH shall notify the SFDA of any new information which may impact the benefit-risk balance of a medicinal product.

XV.C.2.2. Publication of DHPCs

The SFDA may publish the final DHPC. Also, The SFDA may issue an additional safety announcement, and disseminate the DHPC to relevant healthcare professionals' organizations as appropriate. When several marketing authorization holders are concerned (i.e. when the DHPC covers several products with the same active substance or products of the same therapeutic class), marketing authorization holders are strongly encouraged to arrange for one marketing authorization holder to act on behalf of all concerned marketing authorization holders as the contact point for SFDA. Where generics are involved, the contact point should normally be the marketing authorization holder of the originator product. If no originator product is marketed, one of the concerned generic companies is encouraged to act as the contact point. Such coordination between concerned marketing authorization holders aims to ensure that healthcare professionals in Saudi receive a single DHPC covering all the medicinal products affected by a single safety concern (same active substance or a class review). The marketing authorization holder acting as

contact point for the SFDA and on behalf of all other marketing authorization holders should be specified in the agreed communication plan (See GVP Annex III).

GVP Annex II – Template: Direct healthcare-professional communication (DHPC)

<Date>

<Active substance, name of medicinal product and main message (e.g. introduction of a warning or a contraindication)>

Dear Healthcare professional,

<Name of MAH> 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 medicine's 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 MAH/national medicines authority, if applicable>

Further information

<Link/reference to other available relevant information, such as information on the website of a national medicine's 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 national 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>

GVP Annex III - Guide for Marketing Authorization Holders on Joint Direct Healthcare Professional Communications (Joint DHPC) Letter

1. SCOPE

Where there are several Marketing Authorization Holders (MAHs) of the same active substance for which a DHPC is to be issued (innovator and generics, or different innovators/generics, parallels), a single consistent message should be delivered. It should be avoided that healthcare professionals receive several letters with different content from various MAHs. Multiple dissemination may cause confusion in the target population and thus, decrease the effectiveness of DHPCs. Therefore, in these cases, MAHs should participate with each other, and a harmonized content DHPC is distributed to healthcare professionals to enhance patient safety.

This document provides guidance to marketing authorization holders (MAHs) on the submission of Joint Direct Healthcare Professional Communications (Joint-DHPCs) and communication plans to the Saudi Food and Drug Authority for approval and should be read in conjunction with Module XV- Safety Communication in SFDA GVP Guidelines.

This guidance applies to Joint DHPCs that are the subject of a regulatory request in order to promote the safe and effective use of a marketed medicine and to inform healthcare professionals of important new safety information and the need to take certain actions or adapt their practices in relation to a medicinal product if several MAHs are involved simultaneously in the same subject of DHPC.

2. WHEN TO USE JOINT DHPC LETTER

When more than one MAH is involved in the process (e.g. the topic of the DHPC is related to drug interaction, a therapeutic class or equal or more than two registered brand drugs that contain the same active ingredient).

Contribution in a joint DHCP is not mandatory, but refusal of participation is contrary to the

SFDA GVP Guideline recommendations. Nevertheless, if a MAH rejects to participate in the preparation and distribution of the joint DHPC, then this decision should be communicated to SFDA without delay. MAHs who do not contribute to a joint DHPC are still required to prepare and distribute individual DHPCs to targeted group of healthcare professionals (HCPs).

3. PROCESSING OF JOINT DHPC

3.1. ASSIGN COORDINATOR

In order to ensure that the joint DHPC is drafted efficiently and smoothly, it is recommended to designate one of the MAHs as **Coordinator** to align and manage DHPC-related tasks. The designation of the Coordinator should be assigned by SFDA with the agreement of the participating MAHs.

When selecting the Coordinator, the following aspects may be considered:

- The MAH of the innovator product will be the Coordinator
- If there is no inventor, the coordinator will be the first registered generic with marketing status of the product as 'Marketed".

It is recommended that the Coordinator be appointed by MAHs that are involved in the commercialization of their products in the Kingdom. If, despite the above criteria, the MAHs cannot decide who should take the Coordinator role, they should immediately inform SFDA in writing. In this case, SFDA appoints a coordinator.

3.2. Tasks of the Coordinator:

The Coordinator acts on behalf of all the MAHs involved in the joint DHPC as the single official contact point between SFDA and the represented MAHs. It manages and coordinates joint DHPC related activities including:

- Collaboration with involved MAHs on the preparation of the letter content.

- The Coordinator is responsible for the joint DHPC submission to SFDA review and approval.
- Following receipt of SFDA approval, the coordinator forward approved joint DHPC to the concerned MAHs to start its distribution.
- Each concerned MAH shall sign the joint DHPC separately, while the designated Coordinator is responsible for collecting all signatures and submitting them to the Authority as part of the official letter.

3.3. ROLES OF THE CONCERNED MAHs INVOLVED OF THE JOINT DHPC

Upon the SFDA's request, these concerned MAHs should participate with the coordinator in the preparation of the Joint DHPC, the development of the communication plan, the distribution of the DHPC and the verification of the effectiveness of distribution.

Each MAH is responsible for the distribution process of its product based on provided communication/ distribution plan prepared according to the SFDA regulations. Distribution plan should be filled in a standardized form and contain the following:

1. Timetable for disseminating the DHPC
2. The dissemination list
3. The dissemination mechanism

MAHs may use each other's public contact points for communication. In case of difficulty, the Coordinator may contact SFDA for assistance. There is no legal mandate for SFDA to publish a list of national contact points of QPPVs.

4. CONTENT AND FORMAT OF JOINT DHPC

MAHs should follow the guidance provided in the DHPC Template in Saudi GVP Guidelines

Annex II for preparing Joint DHPC letter. Below is the recommended format:

<Date>

<Active substance, (*All brand names marketed active substance of concern*): main message (e.g. introduction of a warning or a contraindication>

Dear Healthcare professional,

< The marketing authorization holders of (Active *substance***) >in agreement with the Saudi Food and 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 medicine's 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 MAH/national medicines authority, if applicable>

Further information

<Link/reference to other available relevant information, such as information on the website of a national medicine's 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 national spontaneous reporting system>

Company contact point

<Table with companies concerned , their Contact point details for access to further information, and for reporting adverse drug reaction including relevant website address(es), telephone numbers and a postal address>

Annexes

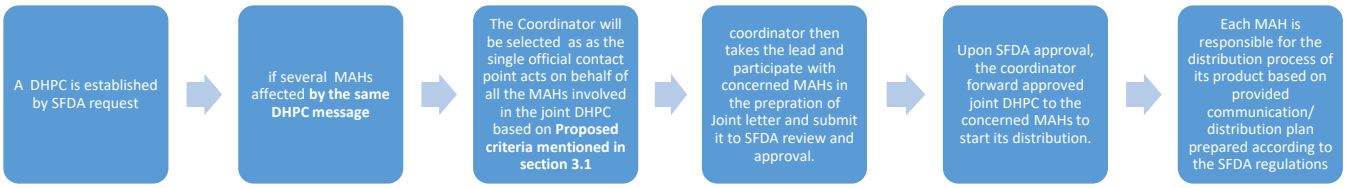
<Relevant sections of the Product Information that have been revised (with changes made visible)>

<Detailed scientific information, if necessary>

<List of literature references, if applicable>

- When there are numerous products and MAHs concerned by a joint DHPC, it becomes challenging to provide such information in a clear and organized way. Furthermore, extensive lists may distract attention from the letter's content. In order to prevent this, the relevant products, MAHs, and contact details should be included in a **separate annex.**

SUGGESTED WORKFLOW



MODULE XVI – RISK MINIMISATION MEASURES: SELECTION OF TOOLS AND EFFECTIVENESS INDICATORS

XVI.A. INTRODUCTION

Risk management includes the identification, characterisation (including quantification), prevention and minimisation of risks. Risk management systems consist of pharmacovigilance activities and interventions relating to individual medicinal products for this purpose, including the assessment of the effectiveness of those activities and interventions. The objectives of risk minimisation are achieved through the implementation of risk minimisation measures (RMM) required by the SFDA and generation of evidence that these measures are effective.

Monitoring RMM outcomes refers to adherence to RMM by healthcare professionals and patients and achieving the objectives of RMM. Monitoring and amending RMM, if warranted, aim at ensuring that the benefits of a particular medicinal product continue to exceed the risks by the greatest achievable margin. The assessment of the effectiveness of RMM is important for risk management with an iterative process of evaluation, correction and re-evaluation of RMM, which is integral to the lifecycle benefit-risk assessment of medicinal products.

This GVP Module should be read together with GVP Module V on risk management systems as documented through risk management plans (RMPs) and on details of routine RMM, GVP Module VIII on post-authorisation safety studies (PASS), GVP Module XV on safety communication and the Addenda of this GVP Module as referenced.

XVI.B. describes criteria for selection, development, implementation and co-ordination of RMM, in particular of additional RMM, and the principles and concepts of the evaluation of RMM effectiveness. XVI.C. describes the related roles and responsibilities of marketing authorisation holders and the SFDA. It also reflects the contribution of healthcare professional and patient representatives.

The term ‘patient’ in this guidance covers patients using or considering the use of a medicine, parents and other carers, and patient and consumer representatives. It also includes the (unborn) child in the case of exposure during pregnancy.

XVI.B. STRUCTURES AND PROCESSES

XVI.B.1. Definition and principles of risk minimisation measures

RMM 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. This includes preventing or reducing the occurrence of adverse reactions due to medication errors

For all medicinal products, risk minimisation is generally addressed by routine RMM. These include the provision of information and recommendations in the summary of product characteristics (SPC) and the patient information leaflet (PIL), the labelling on the immediate or outer packaging of a medicine, pack size appropriate to the usual treatment duration and a risk-appropriate legal status of the product (e.g. prescription-only medicine) (see GVP Module V). For some important risks, however, routine RMM might not be sufficient, and it might be necessary to implement additional RMM.

The risk-benefit balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimising benefits, both through patient selection and treatment management (e.g. specific dosing regimen, relevant testing, patient follow-up). RMM should therefore support the optimal use of a medicinal product in clinical practice with the principal goal of providing the right medicine at the right dose and at the right time to the right patient and with the right information and monitoring.

The selection of RMM and determining whether only routine or also additional RMM are necessary should be based on the characterisation of the safety concerns in the safety specifications of the RMP (see GVP Module V). Each safety concern needs to be considered individually, and the selection of RMM should take into account the seriousness of the identified or potential risk, the severity of the adverse reaction(s), the possible impact of the risk and the RMM on the patient, the preventability and the clinical actions required to minimise the risk as well as the indication, the route of administration, the target population and the healthcare setting for the use of the product. A safety concern may be addressed by using more than one RMM, and one RMM may address more than one safety concern. Additional RMM should be completely separated from

promotional activities.

XVI.B.2. Criteria for requiring additional risk minimisation measures

Most safety concerns are sufficiently addressed by routine RMM (see GVP Module V). Careful consideration should be given to whether the risk minimisation objectives could be reached with routine measures, and only when not considered sufficient, it should be considered which additional measure(s) is (are) the most appropriate. Additional RMM should focus on important safety concerns.

In determining whether additional RMM are needed and which measures would be most effective, marketing authorisation applicants/holders should:

- Consider the target population, frequency, seriousness, severity, context of use, possible impact and preventability of the risk for which the additional RMM is meant to be developed;
- Consider the need for advice to healthcare professionals for appropriate patient selection and excluding patient exposure where the use of the medicinal product is contraindicated, patient monitoring during treatment to prevent adverse reactions or early detection and management of adverse reactions;
- Assess the potential for effectiveness of the additional RMM, including the burden the RMM may impose on the system and possible unintended effects;
- Consider the intended behavioural changes of healthcare professionals and patients during each step of the treatment process; and
- Select the RMM tools that are expected to be:
  - Risk-proportionate and effective in timely manner in minimising the risk;
  - Practical and not too burdensome for patients or the healthcare system.

If several medicinal products, including generics, biosimilars or hybrids, containing the same active substance have been authorised, there should preferably be a consistent approach to developing and disseminating additional RMM coordinated and overseen by the SFDA. Applicants for a biosimilar, hybrid and generic medicinal product should in principle implement the same RMM in terms of content and dissemination as required for the reference medicinal product.

XVI.B.3. Categories and tools of additional risk minimisation measures

A variety of tools are currently available for use on their own or in combined manner as additional RMM. As digital technology advances, the potential of electronic dissemination, such as through web- and app-based mechanisms, allowing for fast dissemination of updated information to the appropriate target audience(s) and for interactions between patients and healthcare professionals, or for safety systems independent from location, may be considered in addition to paper-based materials. Additional RMM can be categorised into the following categories:

- Educational materials;
- Direct healthcare professional communications (DHPCs);
- Pregnancy prevention programmes (PPPs);
- Controlled access programmes.

XVI.B.3.1. Educational materials

An educational material should have a clearly defined scope and objective and add value beyond the SmPC and PL. Although it should not be a mere repetition of the SmPC/PL content or parts of it, it should not relate to safety issues or measures that are not included in the SmPC and PL. The applicable RMM tools described below (see XVI.B.3.1.a.-f.) can be applied on their own or in combination.

Educational materials may have different target audiences, e.g. healthcare professionals or patients. They should be provided in formats and through channels ensuring that the material is readily accessible to the different sub-groups of the target population(s). Educational materials may be helpful for encouraging discussions between healthcare professionals and patients in relation to the safety concerns(s) and RMM when the objectives of RMM cannot be reached with the SmPC and PL alone.

Educational material should be adapted to the target audience. When developing educational materials, it is therefore encouraged, where possible, to engage with healthcare professionals and patient representatives and user-test proposed materials for readability, accessibility, adequacy and user friendliness of formats (e.g. colours, font type/size) as well as of channels in the target population.

An educational material should contain the following information elements:

- Up-to-date, objective, unambiguous and clear statements summarising the nature of the safety concern(s) and the risk and outlining the specific actions to be taken by healthcare professionals or patients in order to minimise the risk and use the product safely (where warranted, information can be provided in more detail or in a different way than in the SPC/PIL e.g. by the use of tables, flow charts or illustrations);
- Guidance for specific actions, e.g. on the prescribing, including indication/contraindication/ patient selection, treatment duration, diagnostic testing, therapeutic monitoring, product handling, preparation for administration, administration, switching to another treatment, or when to seek medical attention in the case of signs or symptoms indicating a possible adverse reaction;
- Reference to the SmPC or the PL whenever possible; in the case of digital educational materials, these could refer to the SmPC or PL through a hyperlink; and
- Statement explaining that this educational material is part of the marketing authorisation and has been approved by the SFDA, including the version date/number and date of approval.

Instructions described in Module XVI Addendum I - Risk Minimization Measures Drafting Guide should be taken into consideration when preparing the materials.

XVI.B.3.1.a. Guides for patients or healthcare professionals for risk minimization

A patient or healthcare professional guide is a tool that highlights the specific actions to take for risk minimisation (see XVI.B.1.) to healthcare professionals or patients.

Typical objectives of such guides include to:

- Enhance awareness of (a) specific risk(s) associated with a medicinal product and (possible) risk factors;
- Guide patient selection;
- Instruct on the prevention, early recognition and timely management of adverse reactions during or after the treatment, including details of enhanced monitoring requirements to aid in the early recognition of certain adverse reactions; or
- Encourage that recommendations in patient guides are discussed by the healthcare professional and the patient when handing out the guide to ensure that the risks and RMM (e.g. need for a diagnostic test, advice on how to prevent medication errors) of the medicine are understood.

Other objectives of patient guides may be:

- Ask the patient to inform the physician about the presence of any/a specific medical condition or concomitant medication before treatment with this medicinal product is initiated;
- Instruct the patient to not attempt to self-treat signs or symptoms of specific adverse reactions or stop treatment without consulting a relevant healthcare professional; or
- Provide guidance on the preparation or administration of the product where these processes are complex, e.g. in the case of patient/caregiver-administered infusions at home.

Although post-authorisation studies and registries are not considered RMM, healthcare professional guides can be useful for reminding healthcare professionals of an on-going registry/study.

In the description of the tool in the RMP, details on the format (e.g. DIN A4 size or larger), its length (e.g. a short or a comprehensive guide) should be specified.

Other terms or publication formats, such as 'brochure', 'sheet', 'patient leaflet', 'slide decks', 'posters' 'dosing guides' or 'induction graphs' should be avoided as synonyms for educational material, and only the term 'guide' should be used to ensure consistency and clarity of the requirements and application of RMM in practice. It is preferable not to add qualifiers to describe the content (e.g. 'administration guide').

XVI.B.3.1.b. Healthcare professional checklists for risk minimization

A healthcare professional checklist is a tool that lists actions aiming to support the prescriber or dispenser to check and record the presence or absence of certain clinical circumstances for risk minimisation. It is to be considered in situations where the safe and effective use of a medicinal product involves complex approaches and decision-making regarding the diagnosis, treatment, prescribing or dispensing, or when the treatment carries a high risk of medication errors.

In contrast to guides (see XVI.B.3.1.a.), a checklist is presented as a series of questions which can

generally be answered in a ‘yes’/’no’/’not applicable’ manner or with a very short answer.

Typical objectives of checklists include to:

- Facilitate determining whether the medicinal product is appropriate for a given patient before or during treatment, e.g. by checking for contraindications, recommendations of use, warnings, concomitant medicine(s) or certain test parameters;
- Ensure any necessary vaccinations before treatment start;
- Exclude pregnancy before/during treatment, record pregnancy testing results, support counselling on the need to avoid pregnancy and therefore use of contraception and support advice in the case of becoming pregnant during treatment;
- Inform about the risk of medication errors and how to avoid them, e.g. by paying attention to selecting the right formulation, checking the strength or dosing against the indication or advising the patient regarding the potential of medication errors;
- Assist in determining the correct amount of product that can be prescribed or dispensed;
- Remind the healthcare professional of the need to monitor the patient for specific signs and symptoms, including specific abnormal laboratory findings, in order to identify adverse reactions early;
- Prompt the healthcare professional to inform the patient about the importance of returning unused product and not sharing the medicine with others, especially for medicines with high risks for other persons or the environment;
- Prompt informing the patient about the importance of not donating blood while taking the medicine; or
- Inform about the need to apply risk awareness forms (see XVI.B.3.1.c.).

XVI.B.3.1.c. Risk awareness forms

A risk awareness form is a tool that informs primarily patients, but also physicians, on (a) certain risk(s) of a medicinal product and the need for risk minimisation. It is also meant to support documenting that the patient has been made aware of the risk(s) during a discussion with a physician and understands the risk and actions to take. It is to be considered in situations where this is essential for using the product. The patient is meant to receive a paper version (or a printout

of an electronic version of the form) from the physician.

Typical objectives of such forms include to:

- Create awareness of specific serious risks e.g. raise awareness about high teratogenicity before and also during treatment, i.e. at the time of repeated prescriptions;
- Reinforce guides for patients and healthcare professionals (see XVI.B.3.1.a.) regarding specific serious risks to further support that the information on risk minimisation in the guide will be read by the patient and be discussed between the patient and physician; or
- Reinforce healthcare professional checklists (see XVI.B.3.1.c.) regarding specific serious risks through documenting that the actions provided in a checklist have been fulfilled and discussed with the patient.

Given these objectives, this tool is likely to be applicable only for very particular risks.

When in a specific local setting formal documentation of the delivery of information for risk awareness to the patient is required at national level, this can take several forms depending on the healthcare system, ranging from a paper or electronic entry in the patient's medical record to using an electronic or paper risk awareness form with a field for the date when the discussion between the patient and physician took place and e.g. a checkbox for confirmation, or, if required nationally, a signature. The form should be provided by the marketing authorisation holder in formats that are adapted to fulfilling documentation purposes in the record management systems of given healthcare systems, as agreed with the SFDA.

Risk awareness forms should clearly state that the patient does not waive any rights by acknowledging the risks. For clarity, risk awareness forms do not transfer the physician's responsibilities when treating a patient to the patient nor do they impact on the patient's rights in relation to the marketing authorisation holder's and healthcare professional's liability.

Depending on the seriousness of the risk and taking into account the need for treatment and typical changes in the patient's situation (e.g. change in the medical condition, risk factors, personal situations such as the wish for a child), it could be useful to consider the need for additional follow-

up risk awareness forms aiming to renew risk awareness of the patient during treatment adapted to typical patient situations.

XVI.B.3.1.d. Demonstration kits

A demonstration kit is a tool that trains healthcare professionals or supports healthcare professionals in training the patient for administering the medicinal product safely. It is to be considered in situations where the administration procedure is complex.

In addition to written or visual material, such kits may contain demonstration objects, such as dummy or demonstrator injectors or inhalers. Demonstration objects should not contain the active ingredient and be clearly marked with “For demonstration purposes only”.

These demonstration kits would typically be supplemented with other aRMM, e.g. guides (see XVI.B.3.1.a.).

Any concern arising from the use of such demonstration kit or indicative of the potential for medication errors when using the medicinal product in real healthcare should be reported to the marketing authorisation holder and, as applicable, to the SFDA. The marketing authorization holder should include reporting advice to healthcare professionals and patients in the instructions of the demonstration kits, investigate such reports and notify the SFDA of any action needed to improve the demonstration kit, the device or product information of the actual medicinal product, and initiate the necessary actions.

XVI.B.3.1.e. Patient diaries for risk minimisation

A patient diary for risk minimisation is a tool that supports the patient in recording specific information on the treatment with the medicinal product. It is to be considered in situations where it is essential that such updated information is regularly exchanged between the patient and the healthcare professional.

Typical objectives of such diaries include to:

- Record dates of administration or dose to avoid medication errors, e.g. in the case of different daily or interval dosing when using the medicinal product in different indications;
- Record dates or outcomes of health monitoring and diagnostic tests at home needed to identify risk factors or signs and symptoms of adverse reactions during continuous treatment to

facilitate monitoring of the patient (e.g. monitoring of blood pressure when taking a medicine with a cardiac risk); or

- Record signs and symptoms indicating a possible adverse reaction, in particular during dose adjustments.

Recording of information for risk minimisation purposes can also occur as part of applying other additional RMM tools, e.g. patients may be asked to record vaccination status, diagnostic test results or dates of product administration on a diary form inside a guide (see XVI.B.3.1.a.) instead of providing it in a stand-alone diary.

Patient diaries for risk minimisation are not primarily meant to be used as a data collection tool by marketing authorisation holders for e.g. PASS. However, information for healthcare professionals regarding a patient diary should remind a healthcare professional who suspects an adverse reaction on the basis of the patient's entries in the diary to report this by using the usual spontaneous reporting systems.

It is to be noted that other patient diaries exist for recording information unrelated to risk minimization but useful for monitoring the efficacy of the product in an individual patient, changes in the patient's physiology (e.g. blood pressure, menstrual cycle), or changes in the patient's lifestyle. However, those patient diaries are not categorised as educational material for risk minimisation and should not be proposed as part of the RMP.

XVI.B.3.1.f. Patient cards

A patient card is a tool that reminds the patient of (a) certain action(s) to take for risk minimisation or aims to ensure that information regarding the patient's current treatment with the medicinal product and its risks is held by the patient at all times and used as a communication aid with healthcare professionals. It is to be considered in situations where it is essential for risk minimisation that this information is always readily available to the patient and healthcare professionals.

Objectives of patient cards include to:

- Remind patients of specific risks and their RMM during treatment, including, if applicable, the need to inform healthcare professionals of this medicine use;

- Alert healthcare professionals that the patient is taking a certain medicine, in particular, those who have not prescribed the product but provide other care to the patient, including emergency care
- Facilitate that the healthcare professional informs the patient about the risk and the actions to be taken for risk minimisation at the intended point of care, i.e. during prescribing or dispensing; or
- Provide contact details of the prescribing physician.

Independently of the objective of a given patient card, other terms, such as ‘alert card’ or ‘reminder card’, should not be used as synonyms for patient card, and only the term ‘patient card’ should be used to ensure consistency and clarity of the requirements and application of RMM in practice.

The content of messages in patient cards may for example cover that:

- The medicinal product is (potentially) teratogenic and requires use of effective contraception;
- Blood donations by the patient are forbidden during treatment and until a certain period has passed after treatment;
- Certain signs or symptoms of the adverse reaction require the patient to seek (urgent) medical care;
- The treating physician needs to be informed of this medication when prescribing other medicines or planning surgeries;
- The device of the medicinal product, e.g. an intrauterine device, should be removed at a specified date;
- Regular monitoring or diagnostic testing is required at specified dates (future medical appointments);
- There is potential for clinically significant interactions with other therapies and that concomitant treatment with those should be avoided;
- The patient on this medicinal product requires additional medication, precautions or other medical procedures to enable necessary surgery or other medical interventions;
- There is the need to avoid vaccination with live attenuated vaccines during treatment;
- It is recommended to read the PL.

Patient cards should be designed so they can be:

- Carried by patients easily, therefore their size should fit inside a wallet or a pocket and ideally have the size of a credit card (if more space is required for content or multilingual requirements, folds can be used; however, for simplicity, as few folds as possible should be used);
- Read and understood easily, therefore, the information provided in the patient card should be focused and concise, kept to the minimum necessary to convey the key message(s); and
- Used over a long time, therefore their material should be of sufficient durability to sustain considerable wear and tear, e.g. be laminated and not be a cut-out or tear-off paper sheet as part of the PIL.

Patient cards should not be presented to patients as a substitute or a small version of the PL or of other educational materials, should they be required for a given medicinal product.

Applicants/marketing authorisation holders should submit a proposal during initial evaluation for how the patient card will be risk-proportionately disseminated for agreement by the SFDA; i.e. whether the card will be distributed inside/affixed to the packaging or outside of the packaging box. Marketing authorisation holders should ensure that patient cards are always available to healthcare professionals when handing over the card to the patient at the applicable point of care (e.g. prescribing or dispensing the medicine). Possible dissemination paths include:

Patient card inside or affixed to the outer packaging:

- Patient cards placed inside or affixed to one of the sides of the outer packaging (e.g. patient card attached to the outer packaging as a flap side with a tear-off section) are considered part of the product labelling. Marketing authorisation holders should ensure that no information on the outer packaging is covered by an affixed patient card. A patient card inside the outer packaging or affixed to the outer packaging ensures that the patient always receives a new patient card with every new package and facilitates the information exchange between the patient and a healthcare professional at the time of dispensing. In addition, it will minimise the

burden for the healthcare professional in terms of maintaining a stock of stand-alone patient cards.

It should however be taken into consideration that the medicine packaging may not reach the patient. If so, further measures need to be taken to ensure that the patient receives the patient card, e.g. in the cases where a medicinal product is administered in hospital settings or in emergency care, or where medicines are repacked at the pharmacy for weekly medication schedules of individual patients.

In the case where the patient card becomes a new requirement in the post-authorisation phase, the marketing authorisation holder may need to take interim measures until the new packages with the patient card are distributed or to allow for dispensing existing pharmacy stock of the medicinal product.

- Stand-alone patient card (separated from the outer or inside packaging):
  If patient cards are provided separately from the packaging, marketing authorisation holders should ensure regular dissemination of a sufficient number of patient cards to healthcare professionals and easy access for healthcare professionals to new stock. In addition, it is recommended to provide healthcare professionals with access to an online request service for additional patient cards and also to online versions of patient cards. Stand-alone patient cards can also facilitate a discussion between the patient and the prescriber independently from the dispensing process of the package.

Whenever more than one medicinal product contains the same active substance and the same messages of the patient card apply to all these products, it is recommended that marketing authorisation holders collaborate on designing and disseminating a single patient card referring only to the name of active substance, and not to any invented name of a medicinal product.

XVI.B.3.2. Direct healthcare professional communications

A direct healthcare professional communication (DHPC) is a safety communication tool that may also serve as an additional RMM. It is to be considered in situations where it is deemed important that all relevant healthcare professionals in the given jurisdiction are timely informed of a risk and actions to take for risk minimisation. Guidance on DHPCs in GVP Module XV should be followed.

XVI.B.3.3. Pregnancy prevention programmes

A pregnancy prevention programme (PPP) is a set of tools that aims at minimising exposure to a medicinal product during pregnancy. It is to be considered in situations where the product has teratogenic effects.

The typical objectives of a PPP are to:

- Avoid that female patients are pregnant when starting the treatment; and
- Avoid that female patients become pregnant during and, if relevant, for a specific period after stopping treatment;
- Avoid, if applicable, that a male patient father a child during and, if relevant, for a specified period after stopping treatment.

A PPP combines the use of different RMM tools and the following should be considered for the development of a PPP:

- Educational material tools (see XVI.B.3.1.) to inform healthcare professionals and patients about the teratogenic risk and the required actions to minimise this risk (e.g. guidance on the need to use appropriate contraception, on the time period during which pregnancy is to be avoided after stopping the treatment);
- Controlled access tools (see XVI.B.3.4.) to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescribing or dispensing of the medicinal product;
- Restriction of amount to be prescribed in a single prescription, often to a maximum supply of 30 days; and
- Counselling in the event of the wish for a child, an unplanned pregnancy or evaluation of an adverse pregnancy outcome.

For assessing the effectiveness of a PPP, organising data collection by means of specific forms for reporting a pregnancy, should it occur, may be part of a PPP.

XVI.B.3.4. Controlled access programmes

A controlled access programme is a tool or set of tools that seeks to control access to a medicinal product beyond the level of control applied to medicinal products by means of routine RMM (see XVI.A.). It may restrict the time period of validity of a prescription or the maximum amount to be prescribed in a single prescription, or require a visual reminder as part of the labelling of the outer

packaging. Controlled access programmes should be considered and applied only in exceptional situations of an important safety concern with a severe impact on the patient or the (unborn) child exposed in utero, or a significant public health impact, taking into account the nature of the risk and the likelihood that this risk cannot be managed by other RMM.

Such programmes should be adapted to local healthcare settings in agreements with the SFDA.

Tools for controlled access, which can be applied on their own or in combination, include the following:

XVI.B.3.4.a. Controlled prescription and supply systems

A controlled prescription and supply system is a tool that consists of a set of measures ensuring that the distribution of a medicinal product is tracked up to the prescription or dispensing of the product. Tracking orders and shipments of product from all identified distribution points facilitate traceability of the product. This tool could also be considered for products controlled under the respective national legislations to prevent misuse and abuse of medicines. For products that need to be prepared for a specific patient (i.e. advanced therapy medicinal products (ATMPs)), further RMM may be needed for ensuring an adequate distribution, storage, preparation, handling and use of the product.

XVI.B.3.4.b. Centre accreditation systems

A centre accreditation system is a tool to ensure that a medicinal product is only supplied to healthcare centres with necessary equipment and healthcare professionals specifically trained to administer the product.

This may be required in specific situations such as for ATMPs or complex administration procedures. Centre accreditation should be organised according to nationally established procedures applicable and be complemented with adequate training of healthcare professionals as agreed with the SFDA.

XVI.B.3.4.c. Forms for patient information exchange between prescriber and dispenser

Different tools are available to ensure that the pharmacist is informed about legally required test results before the product is dispensed, e.g. pregnancy test. This information exchange can take place via paper forms, connected electronic systems or personal confirmation (e. g. dispensing forms, see XVI.B.3.4.d.).

XVI.B.3.4.d. Dispensing forms

A dispensing form is a tool that supports risk minimisation during dispensing. It is to be considered in situations where it is intended to e.g. manage dispensing complex medicines, those requiring certain monitoring or testing within limited time before dispensing or those that require that certain information is transmitted from one healthcare professional to another.

XVI.B.4. Dissemination plans

Marketing authorisation holders should submit distribution plans for the dissemination of RMM to healthcare professionals and patients for agreement by SFDA authorities using a standardized form. The plans should list the RMM tools (see XVI.B.3.), the target audiences, the audience-tailored formats and contents, the dissemination channels (e.g. paper, printable documents, audio, video, web-based, training programmes), use of electronic features (e.g. QR codes, hyperlinks or references), targeted outcomes, timeframes of (re)dissemination for ensuring continuous availability of materials, and supportive communication interventions strategies (e.g. through learned societies or patient organisations). In case of a new marketing authorization, the distribution plan should be submitted once the registration process is completed.

The timeframes for dissemination should consider the needed sustainability of RMM effectiveness over time, both within healthcare professional communities and for individual healthcare professionals and patients. In the case of long-term treatment, periodically repeated delivery of educational materials to a patient may be necessary. Periodic provision of the materials locally is systemically considered at time of implementation. The knowledge adoption and behavioural change of healthcare professional may require repeated RMM interventions in various formats.

XVI.B.5. Effectiveness evaluation of risk minimisation measures

XVI.B.5.1. Principles for effectiveness evaluation

Marketing authorisation holders shall monitor the outcome of RMMs which are contained in the RMP. Monitoring RMM outcomes is intended to evaluate the effectiveness of RMM and may include both routine (see XVI.B.1.) and additional RMM (see XVI.B.3.).

Any study measuring the effectiveness of RMM is a PASS and the guidance for conducting a PASS in GVP Module VIII should be followed for studies evaluating the effectiveness of RMM in addition to the specific guidance in XVI.B.5. The guidance on methods for effectiveness evaluation in GVP Module XVI - Addendum II should be followed and protocols for qualitative studies be included in the pharmacovigilance plan of the RMP (see GVP Module V).

Principle 1: Focused evaluation

Effectiveness evaluation of RMM should focus on RMM of major patient and public health importance, taking into account the nature, severity and seriousness of the risk, the magnitude of population exposure and the amount of public concern.

Principle 2: Regular evaluation

Details of how RMM effectiveness will be measured at regular timepoints should be included in the pharmacovigilance plan of the RMP (see GVP Module V). Several factors will determine the appropriate timepoints, including time since launch or implementation of the RMM, estimated magnitude of exposure, severity and seriousness of the risk(s) and the design of the proposed studies evaluating RMM effectiveness. The following timepoints should generally be considered by marketing authorization applicants/holders for setting timetables:

- After initial implementation of a risk minimisation programme (e.g. within 12-18 months), in order to allow the possibility of necessary amendments;
- Within 3 years of initial implementation of a risk minimisation programme to potentially add further elements to the risk minimisation programme (see XVI.B.5.3.); and
- Within 5 years to assess the overall effectiveness of the risk minimisation programme (see 543 XVI.B.5.3.) or in time for the evaluation of the renewal of a marketing authorisation;

Principle 3: Evaluation of intended and unintended outcomes

RMM objectives should be defined in relation to the targeted dissemination of the RMM as well as targeted changes in knowledge and behaviors or the safe use of medicines by patients, healthcare professionals and organisations providing healthcare. These objectives correspond with the intended outcomes of the RMM and should guide defining the outcomes to be investigated in the evaluation.

As outcomes with a wider impact may occur and unintended consequences may counteract the effectiveness of RMMs, other outcomes of RMM may be investigated where appropriate or upon request of the SFDA (see Table XVI.1.). Unintended outcomes include, for example, undue burden of RMMs on the patient, healthcare professional or healthcare system; decreased prescribing or discontinuation of the medicinal product in patients where the risk-benefit balance remains positive or lack of adherence to prescribed treatment e.g. following risk perceptions amplified by the RMM; switching to another medicinal product with less favourable risk-benefit balance; and spill-over effects due to changes in behaviours beyond the RMM objectives.

Table XVI.1: Effects of regulatory actions on medicinal product use

	Intended	Unintended
Switching	RMM recommends that patients are switched to alternative therapy	Patients are switched to a treatment that has a less favourable safety profile
Spill-over effect	RMM recommends that the treatment is no longer used in a certain patient population and patients are switched to alternative therapy	Treatment is withheld in a patient population that is not targeted by the RMM and where the treatment can be used
Non treatment	RMM no longer recommends the use of a medicine in indications where the therapeutic benefit is no longer considered to outweigh the risks	No alternative medicine is used in some patients of the target population to treat the condition even though alternatives are available
Lack of adherence	N/A	RMM is not adhered to in the target population
Additional	RMM recommends the use of a	RMM no longer recommends the use of

prescribing	medicine in the target population in combination with another therapy (e.g. as preventive measure)	a medicine in the target population, but treatment is continued in combination with another medicine (e.g. to treat adverse reactions) and the recommendation is not adhered to

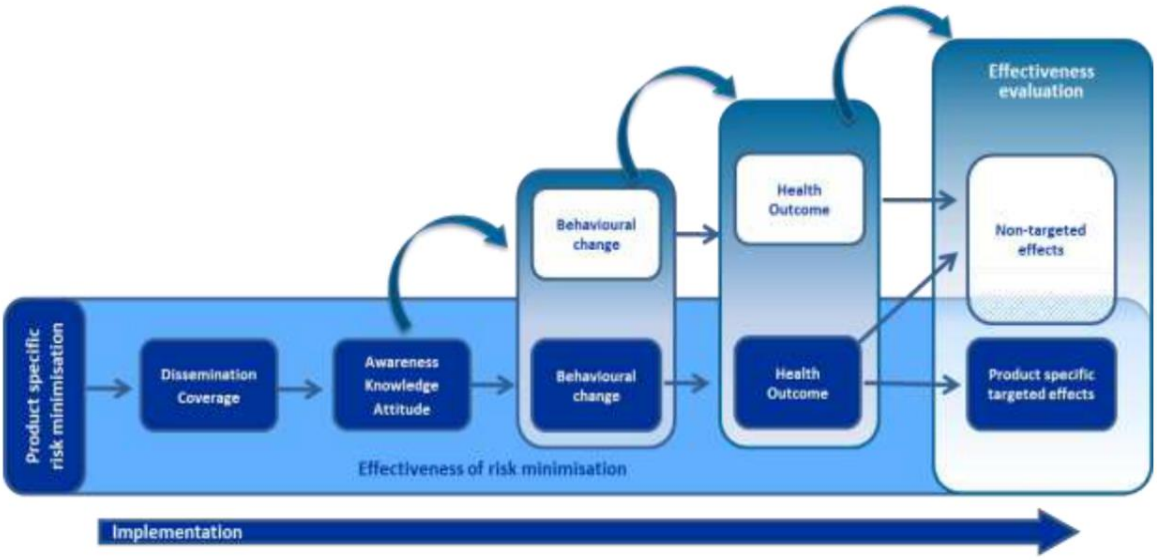
RMM effectiveness evaluation should consider that simultaneous events such as changes in clinical guidelines, reimbursement policies, and media attention may influence the outcome of a regulatory action and make establishing a causal relationship between a regulatory action and its outcomes challenging.

XVI.B.5.2. Objectives and approaches to effectiveness evaluation

In accordance with the principles in XVI.B.5.1. the objectives of effectiveness evaluation are to investigate:

- To what extent the RMM has been delivered to the target audience as planned;
- If the RMM has led to the intended knowledge and behavioural changes in the target audience, or whether other knowledge and behaviour related outcomes have occurred; and
- To what extent the RMM objectives have been met in terms of improved population health within relevant timeframes, or whether other health outcomes have occurred.

Different approaches to data collection and analysis as appropriate may be applied for each step of the RMM implementation process (see Figure XVI.1.). Measurements and indicators of RMM



effectiveness should be defined as part of the study protocol.

Figure XVI.1.: The approach to effectiveness evaluation of risk minimisation includes measuring medicinal product specific targeted effects and, as appropriate, relevant non-targeted effects associated with the use of the concerned and other medicinal products

Depending on the scope of the effectiveness evaluation, a combination of research methods may be useful, and the objectives should be defined in the evaluation strategy in relation to the desired health outcomes of RMM. Marketing authorisation applicants/holders and the SFDA should agree on indicators of success to be included in the evaluation plan. Evaluating the effectiveness of RMM based on quantitative measurements (e.g. prescription or utilisation patterns, health outcomes) is considered particularly important for decision-making on RMM and should be used where feasible. Qualitative research is useful for defining the objectives of quantitative research and understanding the reasons for success or failure of a regulatory action (e.g. observed changes or lack of intended changes in knowledge or behaviours) and its findings may hence be important for considering corrective actions.

The evaluation strategy should consider which methods are proportionate and likely to provide accurate results that are meaningful for further regulatory decision-making without placing undue burden on healthcare systems or patients. The guidance on methods for effectiveness evaluation

in GVP Module XVI - Addendum II should be followed.

XVI.B.5.2.1. Dissemination and risk knowledge

Each stage from dissemination of information on RMM to risk knowledge should be optimised and considered during RMM development and evaluation (see Figure XVI.2.).

Dissemination methods and individual perception of RMM information influence the knowledge of risks. Quantitative measurements of the stages of the communication process may help to identify barriers to dissemination and knowledge adoption, ineffective dissemination processes and knowledge gaps. Qualitative research may help to understand factors influencing risk perception and knowledge adoption.

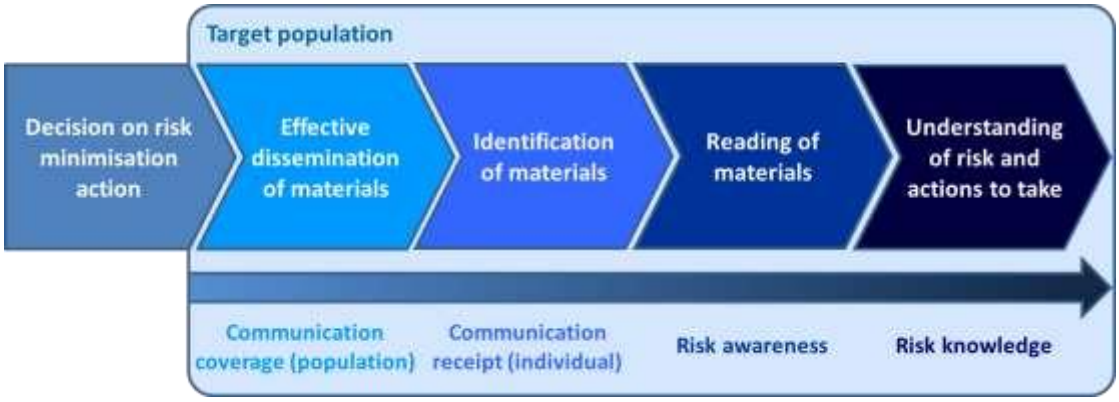


Figure XVI.2.: Pathways of the risk communication process from RMM dissemination to adoption of risk knowledge

Quantitative measurements:

Examples of quantitative measurements of dissemination and knowledge adoption are:

- Proportion of target population for which RMM tool dissemination has been completed over time (in total and e.g. by RMM tool, country or type of healthcare professional) or download total/frequency if electronic tools are provided;
- Proportion of healthcare professionals and patients aware of the RMM and using the educational tools;
- Level of comprehension, recall of information and knowledge of healthcare professionals and patients concerning the RMM tool and its contents.

Qualitative findings:

Examples of outputs of qualitative research into knowledge adoption are:

- Understanding of attitudes about the RMM in terms of e.g. perceived feasibility, acceptability, usability, opinion, motivations, confidence to apply the tool correctly (self-efficacy) and that RMM will be effective in controlling the risk;
- Identification of environmental factors of healthcare systems and patient life impacting on RMM implementation, e.g. resource issues, time constraints;
- Identification of information-related factors influencing knowledge uptake in patients and healthcare professionals, particularly prior information awareness and knowledge of the receiver and communication on the risk from other (preferred) sources.

Risk knowledge may be assessed through qualitative research methods involving case studies, semi-guided interviews and/or focus groups, or through surveys.

XVI.B.5.2.2. Behavioural changes

Based on achieving knowledge on risks and RMM in patients and healthcare professionals, RMM should be developed and evaluated with a view to achieving changes towards intended behaviours of medicines use. Therefore, implementation of RMM in healthcare needs to be feasible and targeted healthcare professionals and patients need to engage and comply with the measures in healthcare and daily routines. Factors that may be enablers or barriers for acquired risk knowledge to result in intended behavioural changes are illustrated in Figure XVI.3.. These enablers and barriers of behavioural change may impact on the feasibility of the RMM in practice.

Quantitative measurements:

Examples of quantitative measurements of behavioural changes are:

- Proportion of patients exposed to a medicinal product in accordance with the authorized indication;
- Proportion of contraindicated patients exposed to a medicinal product;
- Proportion of patients undergoing recommended diagnostic tests (e.g. laboratory, genetic, instrumental) prior, during or after the exposure to a medicinal product;
- Proportion of co-prescribing of two interacting medicinal products;

- Proportion of potential dosing errors;
- Quantification of enablers or barriers for intended behavioural changes;
- Extent to which the user was able to perform and maintain the desired behaviour over time (e.g. prescribing according to the authorised indications or not prescribing in specific contraindications);
- Frequency of requests from healthcare professionals for refills of educational materials or other RMM tools as proxies of RMM tool utilisation.

Behavioural changes may be evaluated through prescribing-, dispensing- and other drug utilization studies, making use of data from electronic healthcare databases or medical records and possibly applying record linkage between different medical and/or demographic data, or through surveys. Quantitative data analyses may also identify enablers or barriers for intended behavioural changes (e.g. healthcare environment factors, availability of resources and processes, access to alternative treatment, healthcare professionals' and patients' perception of a regulatory action and related attitudes).

Qualitative findings:

Examples of outputs of qualitative research into behavioral changes include the identification of enablers or barriers in relation to:

- Awareness (e.g. a new contraindication is not known by some healthcare professionals and/or patients);
- Attitude (e.g. some healthcare professionals and/or patients are not convinced that there should be a contraindication);
- Alternative treatments (e.g. despite the contraindication, some patients still need treatment);

- Difficulties in implementing RMM (e.g. due to lack of diagnostic tools).

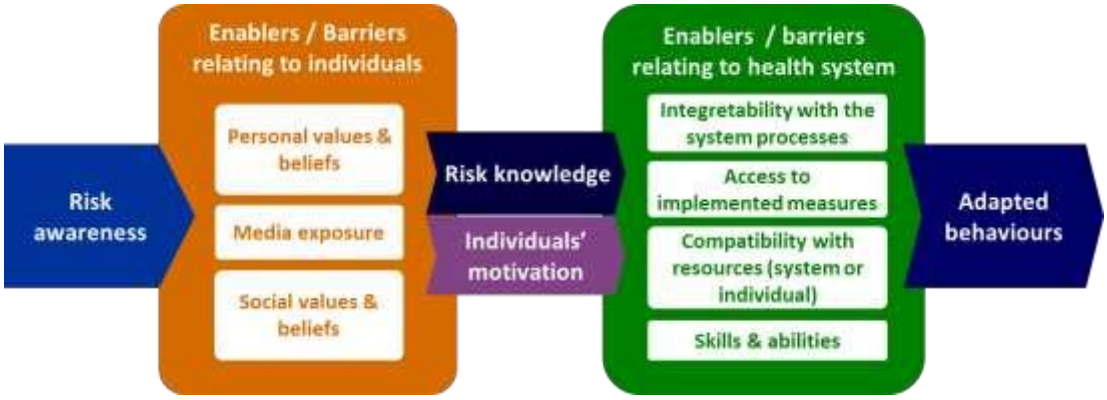


Figure XVI.3.: Pathway from risk awareness to risk minimising behaviors including enablers and barriers of behavioral change

XVI.B.5.2.3. Health outcomes

Monitoring and investigating health outcomes evaluate whether implemented RMM have improved patient and public health.

Quantitative measurements:

Examples of quantitative measurements of health outcomes are:

• Incidence rate or cumulative incidence of an adverse reaction;

• Incidence rate or cumulative incidence of health outcomes of interest, including surrogate endpoints if actual endpoints cannot be measured.

Changes in health outcomes may only be partially influenced by regulatory actions aimed at minimizing risks. Other factors including changes in clinical guidelines or healthcare practices (e.g. monitoring) need to be considered. These factors should be identified and assessed where possible as part of RMM evaluations.

Figure XVI.4. provides an overview of qualitative and quantitative research outcomes that may evaluate the different stages of the implementation process of regulatory actions.

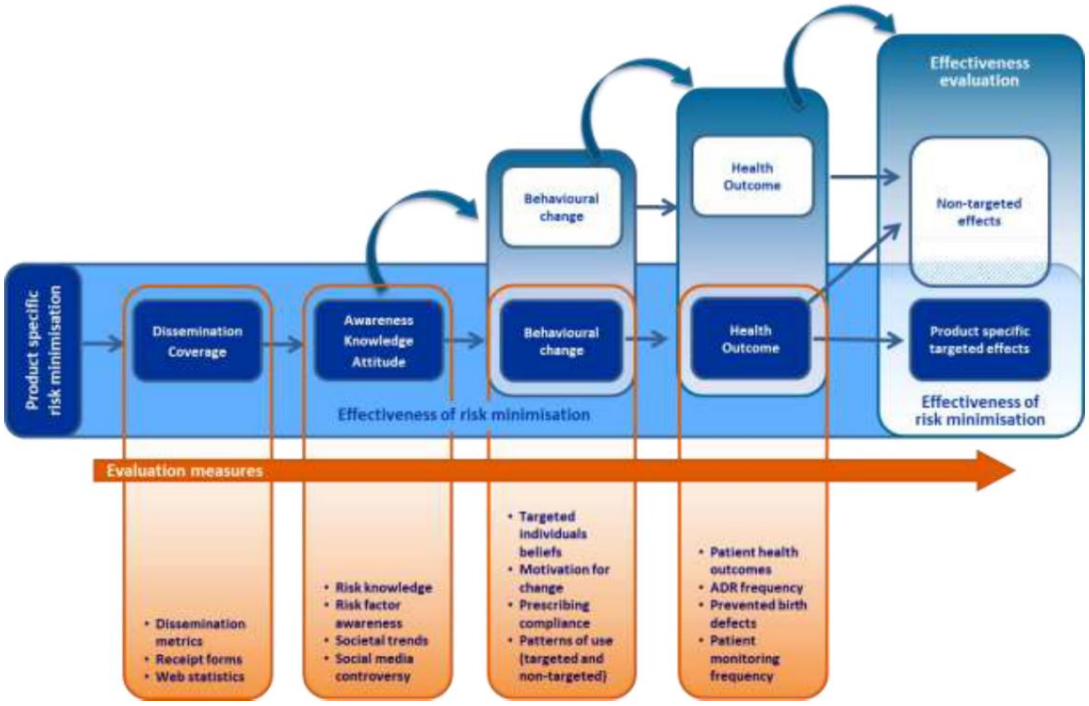


Figure XVI.4.: Approach to effectiveness evaluation of risk minimisation measures showing examples of quantitative and qualitative research outputs at each implementation step.

XVI.B.5.3. Assessment of effectiveness and regulatory follow-up

Evaluating the effectiveness of RMM should provide evidence to regulators to determine whether amendments to RMM are warranted, e.g. through amending the SmPC or PL, clarifying risk minimisation advice, or improving or adding RMM tools (see XVI.B.7.). New evidence on the risk may lead to the assessment conclusion that a RMM tool is no longer necessary. This may for example be the case when more information on the risk being less serious accumulates over time in addition to the evidence on the contribution of the RMM to patient health. Alternatively, there may be reassuring information that the advice contained in the RMM has become standard healthcare and is practiced accordingly in which case regulators may conclude to discontinue the RMM. In some instances, important unintended consequences associated with the RMM (see XVI.B.5.1.) will warrant regulatory action to remedy the situation.

Indicators for success or failure should be determined a priori and on a case by case basis. Threshold values may be defined by using for example baseline or historical data, expected frequency in comparable populations or of comparable risks. Table XVI.3. includes a list of factors

to consider for determining thresholds. The therapeutic context, local specificities (e.g. clinical guidelines) but also other dimensions (e.g. ethical or sociological acceptability) based on input from patient and healthcare professional organisations should be taken into account.

Criteria	
Therapeutic need	• Seriousness of the indication (e.g. life-threatening condition, serious consequences on the quality of life, natural evolution of the disease) • Access to therapeutic alternatives
Population at risk	• Size of the population • Age-group at risk (e.g. children, older patients) • Pregnant women • Frailty • Possibility of taking an informed decision (e.g. access to PL, need for urgent treatment, patients with different chronic disease)
Risk	• Seriousness of the risk (e.g. life-threatening, hospitalisation, reversibility, impact on quality of life) • Novelty of the risk • Risk incidence • Proportion of the risk that can be avoided (risk reduction) • Absolute increase of the risk
Technical possibilities	• Is the level of knowledge to develop a threshold sufficient?
Acceptability	• Benefit-risk balance prior to the new information • Variability between populations • Regulatory acceptability (e.g. previous regulatory decisions for similar risks or medicinal products) • Engagement with concerned patients/carers and healthcare professionals • Level of public interest • Risk level accepted by society (e.g. insurance company, case law, from other technological areas)

Effectiveness evaluation where results indicate that pre-defined thresholds have been reached confirm that the objectives of the regulatory action for a specific product have been met. On the other hand, failure to reach the pre-defined threshold requires further investigation to obtain a clear understanding of the reasons that could help explain the failure. Corrective action to achieve RMM objectives or prevent unintended consequences may include engaging with stakeholders involved in developing clinical guidelines and setting treatment standards.

XVI.B.6. Coordination of effectiveness evaluation across medicinal products containing the same active substance

If several medicinal products, including generics, biosimilars or hybrids, containing the same active substance have been authorised, there should be a consistent approach to planning the evaluation of RMM, overseen by the SFDA, to ensure that the RMM effectiveness can be achieved for each individual product as well as for all products collectively (see XVI.B.2.). However, where RMM for a generic, biosimilar or hybrid product are fully identical with the originator/reference product, there is usually no need to request the marketing authorisation holder of the generic, biosimilar or hybrid product to evaluate RMM for their product (unless agreed otherwise in the RMP). This applies under the assumption that the RMM evaluation strategy requested for the reference product will be able to gather sufficient data. For example, if the introduction of a generic, biosimilar or hybrid product(s) reduces exposure to the reference product, the data underpinning the RMM evaluation for the reference product may become insufficient, and SFDA may also request RMM evaluations for the generic, biosimilar or hybrid product(s).

Where PASS for evaluating RMM effectiveness are required for generic, hybrid and biosimilar products, studies conducted jointly by all marketing authorisation holders (see GVP Module VIII) are encouraged in order to minimise the burden on the healthcare systems. For instance, if a prospective cohort study is instituted, study entry should be independent from the prescription of a product with a specific invented name or provided by a specific marketing authorisation holder. Recording of specific product details may still be important for enabling identification of any new safety hazard with a specific product (e.g. for quality or device defects).

XVI.B.7. Additional risk minimisation measures in the lifecycle of the product

As part of the lifecycle approach, it is also necessary to continuously adapt additional RMM over time and consider their maintenance as appropriate.

RMP for initial marketing authorisations are mainly based on information available from pre-authorisation data, while in some cases, there may be post-authorisation data available if the product has already been authorised elsewhere. Therefore, the information in the RMP at that stage may be incomplete and applicants and regulators might prefer to apply a certain approach at the start of the lifecycle of product and choose to have additional RMM to best address safety concerns that are considered not to be fully mitigated in clinical practice with routine RMM only.

As safety information becomes available with post-authorisation experience, safety concerns (important identified and potential risks and missing information) in the RMP may be reclassified or removed e.g. during the lifecycle of the product, there may be cases where important potential risks that will be further characterised and become important identified risks. With the removal of a risk from the RMP, the need for additional RMM to mitigate this risk becomes obsolete.

There may be a point in time where additional RMM have been implemented in clinical guidance and the healthcare professionals have learned about how to mitigate these risks. In that scenario, a well-known risk is appropriately mitigated and the additional RMM could be discontinued. A regular evaluation for the need of additional RMM is necessary, which should take into account both the effectiveness of the additional RMM and its incorporation in routine clinical practice.

During the lifecycle of the product, the marketing authorisation holder should critically assess whether the materials are still up-to-date with the current knowledge on the safety of the medicinal product.

Where applicable, based on experience and effectiveness evaluations since its implementation and considering current clinical practice, the content, format, layout and distribution modality may be revised or optimised. The RMP should be updated accordingly (see GVP Module V).

Any proposal for reclassification or discontinuation should always be accompanied by a thorough discussion with a due justification about whether the implemented additional RMM needs to be

updated (e.g. strengthening of the wording), enhanced (e.g. introduction of further additional RMM), changed (e.g. patient card instead of prescriber checklist), or discontinued.

XVI.B.8. Quality systems of risk minimisation measures

In accordance to the quality principles detailed in GVP Module I and quality requirements for RMPs of GVP Module V and PASS in GVP Module VIII, the marketing authorisation holder and its qualified person responsible for pharmacovigilance (QPPV) have specific responsibility for the quality, including medical adequacy and scientific integrity, of RMM tools and the quality of the processes for the timely and complete dissemination of RMM to healthcare professionals and patients. For this purpose, the marketing authorisation holder should keep track and record the dissemination process and outcomes.

The marketing authorisation holder is responsible for updating the RMP, including its section on RMM, when new information becomes available.

The MAH should ensure appropriate version control of the RMM indicating the 'last review'-date and ensure that the RMM in circulation are consistent with the authorised product information.

XVI.C. OPERATION WITHIN KSA

XVI.C.1. Roles of the SFDA

The SFDA should monitor and evaluate the outcome of risk minimization measures, including additional risk minimization measures and make recommendations as appropriate regarding any necessary regulatory action. In addition to advising on the studies and measures described in the RMP, the SFDA will assess both protocol and results of imposed PASS which aim to evaluate the effectiveness of risk minimization measures (see Module VIII).

The SFDA is responsible for the oversight at national level of the implementation of additional risk minimization measures imposed as a condition of the marketing authorization for the safe and effective use of a medicinal product in the KSA. For those risk minimization measures introduced after the initial marketing authorization, the SFDA should ensure prompt consideration and agreement of the interventions with the MAH. They should agree the final content, format and

media of the RMM tools, including printed materials, web-based platforms and other audio-video media, availability of materials, as well as the timetable of (re-)dissemination by the marketing authorization applicant/holder before a product is introduced to their market or at any time thereafter as needed.

The SFDA may facilitate harmonization of the implementation of risk minimization tools for generic products of the same active substance. When additional risk minimization measures are considered necessary for generic medicinal product(s) based on safety concerns related to the active substance, the risk minimization measures applicable to the generic product(s) should be aligned with those for the reference medicinal product. Additional risk minimization measures for hybrid products may be required in some circumstances beyond those of the reference medicinal product (e.g. different formulation or route of administration or incompatibility issues).

XVI.C.2. Roles and responsibilities of the marketing authorization applicant or holder

The applicant or MAH should clearly define the objectives of any proposed additional risk minimization measure and the indicators to assess their effectiveness. Any additional risk minimization intervention should be developed in accordance with the general principles outlined in XVI.B.1. and XVI.B.2. and should be fully documented in the RMP (see Module V).

The applicant or MAH should provide information regarding the status of implementation of additional risk minimization measures as agreed with the SFDA and keep them informed of any changes, challenges or issues encountered in the implementation of the additional risk minimization measures. Any relevant changes to the implementation of the tools should be agreed with the SFDA before implementation. For the period of one year after the approval of additional risk minimization measures, the MAH should quarterly provide to the SFDA a report of the distribution process using the standardized form.

For generic products the applicant or MAH should develop risk minimization in line with the scope, content, and format of the tools used for the reference medicinal product. Scheduling and planning of interventions should be carefully coordinated in order to minimize the burden on the

healthcare systems.

For generic products, the effectiveness of risk minimization measures should be assessed by the MAHs in close cooperation with the SFDA. Where formal studies are justified, joint studies for all medicinal products involved are strongly encouraged in order to minimize the burden on the healthcare systems. For instance, if a prospective cohort study is instituted, study entry should be independent from the prescription of a product with a specific invented name or MAH. Recording of specific product details would still be important to enable rapid identification of any new safety hazard with a particular product.

The MAH shall monitor the outcome of risk minimization measures which are contained in the RMP. General principles for effectiveness evaluation are provided in XVI.B.5.

The applicant or MAH should report the evaluation of the impact of additional risk minimization activities when updating the RMP (see V.B.11.4.).

The applicant or MAH should report in the PSUR/PBRER the results of the assessment of the effectiveness of risk minimization measures which might have an impact on the safety or benefit-risk assessment (see VII.B.5.16.5. and VII.C.5.5). The applicant or MAH should ensure timely communication with the SFDA for relevant regulatory evaluation and actions, as appropriate (see also XVI.C.2. and Modules V and VII).

XVI.C.3. Collaboration with healthcare professional and patient organisations

The contribution from healthcare professionals and patients is of paramount importance for the decision-making of the SFDA, to ensure that RMM are adequate to address the risk and feasible, and do not create an undue burden to patients, healthcare professionals and the overall healthcare systems. Patients' and healthcare professionals' contributions are considered to optimise the development of RMM tools by bringing their real-life experience of disease management and medicines' use into the regulatory assessments. This should also ensure that any RMM is able to overcome the barriers often encountered in the process of their implementation in healthcare due to the characteristics the local healthcare system.

Where possible, it is encouraged that the SFDA, as applicable, engage with healthcare professionals and patient representatives for obtaining their contributions and discussing:

- Current awareness, understanding and management of the potential risks of the medicine;

- Effectiveness, appropriateness and feasibility of having additional RMM in place;
- Most efficient risk minimisation tools and appropriate and feasible dissemination processes in relation to target audience(s) and channels;
- Support for healthcare professional and patient organisations by means of e.g. clinical guidelines, patient guides made available by healthcare systems or patient organisations, articles in scientific journals and conferences; and
- Other practical suggestions for improvement.

XVI.C.4. Impact of risk minimization measures effectiveness on RMP/PSUR/PBRER

PSUR/PBRER and RMP updates should include a summary evaluation of the outcome of specific risk minimization measures implemented to mitigate important risks in the KSA. In the RMP, the focus should be on how this informs risk minimization and/or pharmacovigilance planning. In the PSUR/PBRER, there should also be evaluation of how the implemented measures impact on the safety profile and/or benefit-risk balance of the product. In general, the focus should be on information which has emerged during the reporting period or since implementation of the most recent risk minimization measure(s) in the KSA. Where there is parallel submission of a PSUR/PBRER and an RMP update, the use of a common content Module should be considered (see GVP Modules V and VII). For the evaluation, the guidance in XVI.B.5. applies.

MODULE XVI ADDENDUM I - RISK MINIMIZATION MEASURES DRAFTING GUIDE

Xvi.add. I.1. Introduction

Risk Minimization Measures are public health 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.

Risk Minimization Measures include:

- **Educational materials** such as healthcare provider guides, prescriber checklists, or patient alert cards.

Educational programs are additional risk minimization measures (RMM) (see GVP Module XVI) and usually require educational materials based on targeted communication with the aim to supplement the information in the summary product characteristics (SPC) and package Information leaflet (PIL).

When the development and distribution of educational material is recommended by the SFDA, a draft of educational materials should be submitted to the SFDA and these educational materials shall implement the key elements. Alternatively, the exact content of educational materials could be agreed and also become part of the summary of product characteristics (SPC) and/or the package Information leaflet (PIL), as applicable.

- **Direct Healthcare Professional Communications (DHPCs)** which are communication interventions aimed to deliver important information directly to individual healthcare professionals by the marketing authorization holder (MAH) to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product.

The aim of this Addendum is to provide general guidance on the local requirements for drafting educational materials and Direct Healthcare Professional Communication (DHPC) letters that are part of Risk Minimization Measures.

Xvi.add. I.2. Documents that should be submitted with the RMM:

- The latest copy approved or on approving process of Saudi summary of product characteristics (SPC) and Patient Information Leaflet (PIL).
- An Arabic version of the educational material if it is directed towards patients.
- In case of submitting a RMM for updating the RMM contents, the differences between it and the previously approved version should be clarified and highlighted.
- A certified translation into Arabic of the educational materials, in case they are directed to patients.

Xvi.add. I.3. Principles for educational materials:

XVI.Add.I.3.1 General principles:

- The need for educational materials will be agreed during a regulatory procedure, at the moment of the initial marketing authorization or in the post-authorization phase.
- Any educational material should focus on the risk minimization objectives.

- It should not be combined with promotional materials for the marketing of the medicinal product.
- When the need for educational material is agreed, the dissemination of the educational material is mandatory. The modalities for dissemination and the target audience should be described in the distribution plan (XVI.Add.I.5.).
- The MAH should exercise version control and ensure that it disseminates only the latest agreed version of the educational material.
- Applicants/marketing authorization holders for the same active substance may be required by the SFDA to have educational material with as similar as possible layout, content, color and format to avoid patient confusion.

XVI.Add.I.3.2. Requirement for the content of educational materials:

- The content should be prepared based on the most current scientific evidence available.
- The content should focus on the specific safety concerns and provide clear statements and concise messages describing actions to be taken in order to prevent and minimize these risks.
- Additional information such as efficacy data, comparisons of safety with other medicinal products or statements that imply that the medicine is well tolerated should not be included.
- The indication for the medication should be included with the exact wording mentioned in the Saudi SPC. However, if the material is directed towards patients, a suitable wording should be used instead.
- Start with objectives of the document. A statement explaining that the educational material is essential to ensure the safe and effective use of the product and appropriate management of the important selected risks.
- A statement encouraging reading the document, such as “It is advised to be read carefully before <prescribing/dispensing/administering> the product.” is preferred to be added.
- In order to avoid repetition of SPC and/or PIL texts, the messages in the educational material should complement the SPC and/or PIL based on the agreed key elements. Including an exact transcript of the text of the SPC/PIL should be avoided.
- The educational material should be kept as brief as possible, however, if the educational material is long, an introductory text summarizing the key messages should be added and an index may be included.

- The inclusion of promotional elements, either direct or veiled (e.g. slogans, product brand colours, promotional images and pictures) is non-acceptable.
- Referring to other medicinal products outside the scope of the educational material should be avoided.
- Avoid using scientific, medical and complex words as possible; explain them when they cannot be avoided; explain all abbreviations and acronyms.
- A statement referring the reader to the SPC or PIL for further information should be included.
- The Saudi SPC and/or PIL may be attached to the educational material and disseminated together.
- The educational material may contain a reference to a website containing the Saudi SPC and/or PIL, or a website designated for the SFDA-approved RMM. However, reference to other regulatory authorities' documents or websites will usually not be accepted.
- A statement clarifying that the document is approved by the SFDA should be added.
- A statement encouraging ADR reporting to the MAH and SFDA should be added. Together with the local contact information of the MAH and Saudi Food and Drug Authority's National Pharmacovigilance Center.

  National Pharmacovigilance Center (NPC) - Saudi Food and Drug Authority
  SFDA call center: 19999
  E-mail: npc.drug@sfda.gov.sa Website: http://ade.sfda.gov.sa/

XVI.Add.I.3.3. Requirement for the format of educational materials:

- The title of the documents should be clear at the top of the first page.
- The title should mention statement similar to "Important Safety Information" or "Risks associated with the use of the product" or "Important Risk Minimization Information for <Healthcare Professionals, Patients>".
- The title should include the invented "brand" name and the active substance of the product.
- An additional title line should be added to identify the type of educational material (Physician guide, Patient reminder card … etc.).
- The first page can include the photo of the medicinal product pack.

- Bullet points should be used wherever appropriate to present the information clearly.
- The invented "brand" name should only appear where strictly necessary and the number of times the invented names appears in the educational material should be limited.
- If the logo of the MAH appears, the logo should appear only once on each educational material, preferably on the last page. If it appears on the first page, the logo should not be larger than the title.
- The version number and the date of drafting the material should be added in the format of "<month> <year>" on each page of the educational material.
- A statement clarifying whom to contact when extra copies of the material are needed should be included. For instance, "For extra copies please contact (MAH contact number)".
- The first draft of the aRMMs should be submitted in a word format or readable pdf.
- After the initial approval of aRMMs content, MAH should submit a designed aRMMs for final approval.

XVI.Add.I.3.4. Patient Risk Minimization Measures:

- Patient directed educational materials should be available in both Arabic and English languages.
- Reading level of the materials should be suitable for targeted audience, using tools to measure reading level such as the Flesch-Kincaid readability tests is recommended.
- Factors including reading level, cultural background, age, and language must be considered during drafting the educational material.
- The educational material should be attractive and appealing, using appropriate images for instance to draw attention to the most important messages.
- Using illustrations, symbols, pictographs, and other visuals that are related directly to the information is encouraged to reinforce key messages.

XVI.Add.I.3.5. Requirements for Arabic versions of patient educational materials:

- In addition to the guidance described above for patient risk minimization measures, the following should be considered while drafting Arabic versions of patient educational materials;
- Arabic version should be translated through certified translation.

- Simple and straightforward sentences should be used.
- The educational material should be free from grammatical errors and misspellings.
- While translating the educational material, complicated medical terms should be avoided and substituted with simpler terms. If a medical term has to be mentioned, it should be explained briefly and the English term could be stated.
- The invented "brand" name and active substance should be mentioned in Arabic.

Xvi.add. I.4. General requirements for direct healthcare professional communication (DHPC):

- The first draft of the DHPC should be submitted in a word format.
- When drafting a DHPC, the template (see GVP Module XV Annex II should be followed as appropriate:
  - The document must be titled "Direct Healthcare Professional Communication" then includes the active substance, the name of medicinal product and the main message (e.g. introduction of a warning or a contraindication).
  - A statement indicating that the information is being sent in agreement with the Saudi Food and Drug Authority should be added.
  - The date of drafting the DHPC should be included at the top of the letter (Left side).
  - The DHPC should include a section titled "Summary" to include a brief description of the safety concerns and recommendations.
  - The DHPC should include a section titled "Further information on the safety concerns and the recommendations" where important details about the safety concerns and the recommendations are written.
  - The DHPC should include a section titled "Call for reporting" where ADR reporting is encouraged and the MAH and SFDA reporting contact information is provided.
- The title should be well-addressed and the risk or safety concerns is clearly mentioned.
- The name of the MAH should be included.
- If the DHPC is adapted from a foreign regulatory authority, the submitted local DHPC should be reviewed and modified to reflect local and current situation in Saudi Arabia.
- The letter should not contain any promotional statements.

- The final version of the DHPC should be provided in a true searchable pdf format and singed electronically by the local QPPV or the person in-charge with his/her title written.
- References should be provided with the DHPC if feasible.

Xvi.add. I.5. Distributing and implementing RMMs and DHPCs:

Marketing authorization holders are responsible for distributing the approved RMMs and maintaining its availability in institutions where their product is available.

- Prior to the distribution of any RMMs (including DHPCs), a distribution plan must filled and submitted for review and approval by the SFDA. In case of a new marketing authorization, the distribution plan should be submitted once the registration process is completed.
- The MAH are requested to complete the distribution of Direct Healthcare Professional Communication (DHPC) letters within 60 days after its approval. An evidence of the distribution must be submitted after the completion of the distribution using the standardized form. If the DHPC is distributed electronically, the distribution process should be completed within 10 working days.
- An evidence of the distribution process of Risk Minimization Measures other than DHPCs must be submitted quarterly, for the period of one year, using the standardized form. If the measures is distributed electronically, the distribution process should be completed within 10 working days.
- After one year from starting the distribution process (i.e. after submitting four distribution reports), the MAH is no longer required to submit further distribution evidence. However, it is still the MAH's responsibility to ensure that the RMMs are continuously available in enough amounts wherever the product is prescribed and dispensed. In addition, the MAH should submit the distribution evidence, when including institutions where the product is added recently and was not covered in the initial distribution plan.
- RMMs shall not be removed or discontinued, unless the MAH updates the Risk Management plan (RMP) of the product and provides a rational for its removal.

Xvi.add. I.6. Publication of risk minimisation measures:

Approved RMMs and DHPCs will usually be published in the SFDA website.

XVI.Add.I.6.1 Publication of educational materials on MAH on specific websites

When agreed by the SFDA, the MAH may publish educational materials on a specifically dedicated website, provided that the MAH respects the following:

- Access to the website should be given to the SFDA;
- A statement that the information of the website is consistent with the agreed material should be submitted;
- The specific website should not include any reference to documents or to other websites/pages or weblinks not agreed by the SFDA;
- All elements and information on the specific website should be expressed in the official language(s) as required by the SFDA;
- The specific website should not contain references to or information about medicinal products not marketed in the KSA.

Other relevant documents such as the Saudi SPC, the PIL and the summary of the RMP may be referred to.

Xvi.add. I.7. Considerations for drafting patient communication:

The ideal structure that can used in the communication with patients (and general public) is illustrated in the table below; the first section is primary content that is essential; the second section is discretionary and could be excluded if there are good reasons to do so.

Section	Text elements	Explanation, guidance and examples
Section 1: Primary content		
Heading and sub-heading	• Description of the purpose of the message • Explain the following: ○ For whom is this message? ○ What information they need to know. ○ Action to be taken.	Headline examples: • Important [New] Safety Information for patients taking XXX (the product) • Risks associated with the use of XXX • New guidance for safe prescribing of XXX Sub-heading examples: • Do not use when pregnant • Check your blood-pressure regularly • Be alert for muscle pain • Do not use at doses above 20mg

Critical elements of the message	**Essential information** This is the most important part, explain the purpose of communication "If you read nothing else, read this" The product [simple version, common name] and its principal indications Who is this for? What is the risk? What action to take?	This should be presented as bare-bones bullet points formatted to make it stand out (e.g. in a box or panel) The principles apply whatever the category of message; the specific items in the list may change for different purposes The 'audience' is the target segment of patients or HCPs (or both)
Expanded version of the core message	**Explanation** • Summary of the safety issue • Nature of the risk • Seriousness • Precautions • Warnings	This material should be as brief and condensed as possible, presented in minimal short sentences under the bullet points. Provide minimal data and information about frequencies, seriousness, etc.
Evidence	**Evidence and rationale**	Brief statement of what has happened to make this communication necessary
Points for Action	**Advice for action**	Repeat of headline message and desired response. SFDA recommendations and advice for risk minimisation in relation to the risk or safety concern. Recommendations on how to manage other concerns. For example: when a withdrawal decision is issued, the method of safe behavior for the patient should be clarified such as: • 'Do not stop taking the drug before consulting a doctor at the earliest opportunity, or going to your nearest pharmacy and finding out about alternatives.' Or, if the warning is about a new adverse effect: Monitor your health for any sign of [adverse effect] and consult your doctor if anything worries you.
Response options	**Share information and ask questions** • If you have comments or concerns about your medicines contact your doctor or pharmacist or SFDA ○ [SFDA contact] • If you have any side effect from a drug, use the SFDA reporting process and help us understand more about your medicines ○ [ADR reporting link]	

ADR reporting promotion	**Help us keep patients safe** Report any adverse effects you experience from any medicines. SFDA can help keep everyone safer if you let us know your concerns. This is how you report adverse reactions – it is simple and quick: XXXXX	This is a slightly fuller version of the invitation suggested above
Section 2: Secondary supportive information [optional]		
Additional information	**Further information**	This section can include anything not covered in Section 1 that the enquiring patient or HCP might like to know or that SFDA feels should be in the public domain but is not essential to safety and rational use (that should all be in Section 1) Topics such as: • Reversibility of potential adverse reactions • Expected time to recovery • If possible and available, add reference to where further information about the risk can be found • Additional risk factors • Therapeutic indications • Dosage and administration issues
Other sources of information	**Where to find more information**	Websites or other links for the thorough investigator

MODULE XVI ADDENDUM II – METHODS FOR EFFECTIVENESS EVALUATION

XVI.ADD.II.1. Introduction

This Addendum to GVP Module XVI provides additional guidance for marketing authorisation holders and SDFA on data sources and methodologies for monitoring outcomes of risk minimisation measures (RMM) in line with the principles for RMM effectiveness evaluation laid down in GVP Module XVI.

Depending on the risk minimisation objective, studies evaluating RMM effectiveness may integrate different quantitative measurements and qualitative research approaches to evaluate risk minimisation outcomes for individual tools or sets of RMM described in GVP Module XVI. Risk knowledge, behavioural changes and health outcomes may be considered, and in this respect the guidance on objectives of effectiveness evaluation in GVP Module XVI should be followed. The Addendum also provides guidance on the reporting of the results of studies evaluating the effectiveness of RMM.

XVI.ADD.II.2. Data collection

Depending on the context and objectives of RMM effectiveness evaluation, primary data may be specifically generated to evaluate effectiveness, or secondary (pre-existing) data originally collected for other purposes may be used. A combination of primary and secondary data sources may be considered to evaluate effectiveness more comprehensively.

Relevant information on clinical actions including prescribing behaviour and health outcomes may be extracted from routinely collected data in electronic healthcare databases of (electronic) medical records or administrative claims records, for secondary data analyses (1–3). Suitable electronic healthcare databases are described in the literature (4).

XVI.ADD.II.2.1. Data sources

XVI.ADD.II.2.1.1. Qualitative research

Common data sources for qualitative research in healthcare are interviews, focus groups and different existing types of documentations (e.g. media reports or clinical guidelines), as they may contain information about cognitive processes and experiences of patients and healthcare professionals.

The type of documentation to use as data source for understanding perception and information needs in certain patient or healthcare professional populations will be determined by their media preferences. Preferences for e.g. news, social or scientific media can be identified through qualitative or quantitative media research.

The recruitment of participants in focus groups or interviews, or the selection of documentation is aimed at saturation of data, so that they provide for a robust understanding of the cognitive processes and experiences that are typical in the population of interest, and also cover less common views or needs of sub-populations of patients and healthcare professionals. Therefore, diverse participants should be selected for their ability to provide in-depth insights. Appropriate sampling is a key requirement to obtain relevant information and minimise bias, and to achieve study results of high quality that can provide findings that are applicable to the whole population of interest. The sampling strategy's target is relevance of the information to be collected, and various strategies can be applied: representative sampling in relation to certain criteria describing the population of interest, complete sampling to include all concerned people within a defined region or timeframe, or step-by-step sampling to identify all themes or investigate emerging themes more in depth (5–7). The appropriate sampling strategy should be adapted to the diversity of the patient or healthcare professional population of interest and recruit also those who may be less proactive to participate in such research.

Data collection through interviews or focus groups should preferably use open questions and can be conducted with variable degrees of structure, depending on the study objective and the available evidence on the topic to be studied (8–10). Studies should be conducted to standards that avoid expected-response bias.

XVI.ADD.II.2.1.2. Surveys

Surveys are a method to collect primary data from a sample of a population and typically apply a standardised questionnaire through in-person interviews or options for self-reporting with postal mailings or electronic communication (e.g. web panels). These may be supported by audio computer-assisted self-interviewing (A-CASI) or interactive voice response systems (IVRS). The choice of the most suitable data collection approach will depend on the target population characteristics, the disease and the treatment characteristics, and the type of data to be collected.

For a healthcare professional survey, participants may be recruited from web panels and member lists of professional and learned societies. For patient recruitment, the relevant clinical setting and

existing web-panels should be considered as well as members of patient organisations.

A survey may be conducted to evaluate dissemination of RMM tools, risk knowledge and behavioral changes provided adequate survey methodology (see XVI.Add.II.3.2.) is applied.

Important limitations to be considered are poor sampling strategies and low response rates that may introduce bias (see XVI.Add.II.3.2.). Surveys often collect and analyse self-reported data, thus introducing misclassification of exposure or the Hawthorne effect, i.e. respondents may improve or modify an aspect of their behavior in response to their awareness of being observed.

XVI.ADD.II.2.1.3. Registries

Patient registries organised systems that collect data and information on a group of people defined by a particular disease or condition, and that serve a pre-determined scientific, clinical and/or public health (policy) purpose.

Registries play an important role for monitoring the use of medicines or health services, or medical conditions, and hence for evaluating RMM in terms of behavioral changes or health outcomes.

Behaviors relevant to RMM include for example change in prescribing patterns, usage of diagnostic tests identifying risk factors for adverse reactions or attending teratogenic risk counselling. Registries may be beneficial for collecting data for specific populations such as patients with rare diseases, patients that require highly specialised health interventions or pregnant women. Some registries collect additional information, such as lifestyle factors, smoking, alcohol use, nutrition and weight, which may be risk factors for certain adverse reactions and can hence help evaluating adherence to RMM addressing these risk factors. The financial and administrative burden and time effort for setting up tailor-made registries may limit their use solely for RMM effectiveness evaluation and give preference to acquiring access to existing registries for secondary data analysis. Important limitations to be considered are low accrual rates, data quality issues or missing data (11, 12).

XVI.ADD.II.2.1.4. Medical records

Electronic medical records should be considered for effectiveness evaluation of RMM to be implemented in primary care (general practitioner and community services) and/or secondary care (hospitals and specialists) (4) for their rich clinical details such as diagnoses, procedures, laboratory values and health outcomes. Medical records are a suitable source for measuring changes in prescribing behavior, but the feasibility of obtaining and measuring health outcomes in

electronic medical records largely depends on the type of outcome, the seriousness of the adverse event and coding practices, e.g. for laboratory test results. Where relevant outcome variables are not routinely collected, complementary primary data collection may be considered. Compared to administrative claims data, medical records do not capture whether the prescribed medicine has actually been dispensed (see XVI.Add.II.2.1.5.). A limitation is that the actual administration and use of the medicine by patients cannot be verified.

XVI. ADD.II.2.1.5. Administrative claims

Administrative claims data are generated by healthcare systems for insurance purposes and cover the entire or a subset of insured patients. Claims data usually capture information from all physicians and care providers for the insured patient and are normally well suited for drug utilisation studies as they record prescriptions at the time of dispensing, i.e. they record that the patient has obtained the medicine, although they cannot record whether the medicine has actually been taken, at which dose and in which way. Different reimbursement policies between countries and policy changes over time may impact the data source's suitability for evaluating the effectiveness of a RMM.

A major limitation of administrative claims data is that information not relevant for billing purposes is not documented, such as laboratory values, results of imaging and other diagnostic procedures, prescriptions not submitted or eligible for reimbursement and self-medication including over-the-counter (OTC) products. Furthermore, information on inpatient medication and diagnoses made in hospitals may not be available.

XVI. ADD.II.2.1.6. Healthcare record linkage

Healthcare record linkage systems bring together information from multiple data sources at the level of individual patients, expanding data that is not captured in the initial data source. For example, dispensing data may be linked to cancer- or other registries. Data linkage is regulated to ensure that ethical standards and personal data protection regulation are adhered to.

XVI. ADD.II.2.1.7. Spontaneous reports of suspected adverse reactions

Interpreting data from spontaneous reporting of suspected adverse reactions for the purpose of RMM effectiveness evaluation needs to take into account i) general underreporting of adverse reactions; ii) increased risk awareness due to the RMM possibly leading to increased reporting; iii)

the Weber effect, which describes a frequently seen decline in reporting once an adverse reaction of a medicinal product becomes well-known; and iv) the lack of precise data on the exposure to medicinal products for calculating reporting prevalence. Therefore, comparing trends in spontaneous reporting of events of interest for the targeted medicinal product or product class with alternative products is not considered adequate for demonstrating that RMM has been effective. However, in specific situations, the continued spontaneous reporting of a very serious adverse reaction despite RMM may be taken as supportive evidence indicating that the RMM may not be effective in combination with evidence from non-interventional studies (see XVI.Add.II.3.3.). Spontaneous reporting may also be useful to identify risk factors for adverse reactions in relation to how medicines are used, e.g. in the context of medication errors.

XVI. ADD.II.2.2. Factors influencing the choice of data source(s)

The choice of data source(s) for effectiveness evaluation should be determined by the following factors:

- Scope and research question: Good understanding of eligible data sources to verify whether information answering the research question is available (e.g. secondary use of routinely collected data were not designed to answer the research question) and its strengths and limitations should be considered in the design of studies evaluating effectiveness.
- Accessibility of data sources: Access and conditions for collaboration with data source owners should be clarified.
- Information on exposure and outcome: The reliability of information on exposure and outcome in the data source under consideration should be verified.
- Availability and timeliness: Pre-existing data is more likely to be readily available for analysis compared to primary data collection, and timelines for the entire process from data delivery to availability of secondary use data and lag times should be considered.
- Prevalence of outcomes of interest: Routinely collected data tends to have large sample sizes which may be relevant for rare exposures and rare outcomes.
- Observation period: For detecting changes over time or delayed effects of RMM, data must be collected over a sufficiently long period of time. As the complete medical and clinical history may not be available in databases, the extent of left and/or right truncation should

be considered, for example if no information is available outside of the respective insurance period in case of claims data.

- Representativeness of the study population: The representativeness of the study population for the entire population should be assessed. For example, where claims databases are used, the population with a specific health insurance may be inherently different to the entire population, which may introduce bias. Survey studies are prone to selection bias that may affect the generalisability of results. In case of evaluating non-targeted effects, the study population should preferably not be limited to the population targeted by the product-specific regulatory action (see GVP Module XVI, Figure XVI.1.).
- Completeness of the data: The amount of missing or incomplete variables should be considered where data was initially collected for a purpose different from the research question, for example indication of medicines use, co-morbidities, co-medication, patient monitoring, smoking, diet, body mass index or family history of disease.

XVI. ADD.II.3. Research methods

Figure XVI.Add.II.1. shows relevant methods and study designs for evaluating the effectiveness of RMM, considering each step of implementation process.

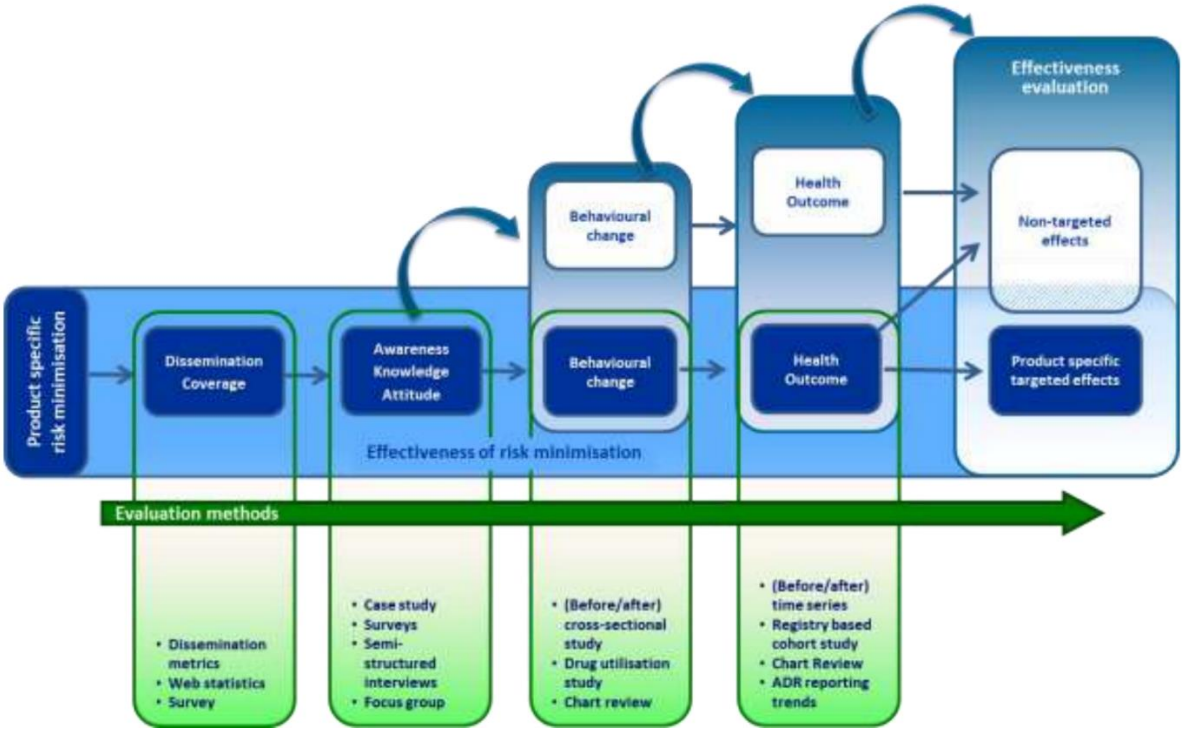


Figure XVI. ADD.II.1: Overview of quantitative and qualitative methods for evaluating effectiveness of risk minimisation measures at each step of the implementation process (Note: Effectiveness evaluation includes measuring medicinal product-specific targeted effects and, as appropriate, relevant non-targeted effects associated with the use of the concerned and other medicinal products (see GVP Module XVI, Figure XVI.1.).)

XVI. ADD.II.3.1. Qualitative methods

Qualitative research plays a distinctive role in evaluating healthcare interventions (13), especially on issues not yet well understood (8,9). It can study cognitive processes and experiences in their natural setting, such as knowledge, risk awareness, trust, reasoning processes and attitudes about medicines, communication needs and preferences, and experiences of using medicines in real life. Enablers and barriers for implementing RMM in healthcare and for achieving behavioural change may be identified through qualitative research.

Qualitative studies may generate concepts or hypothesis to be further investigated through quantitative research and inform protocols for quantitative studies. Qualitative studies may also explore explanations and reasons for results from quantitative research (14) and identify reasons other than the RMM leading to the outcomes of interest.

Among the various possible study designs (15), the following are well-established and particularly relevant for evaluating RMM:

- Interpretative phenomenological study: investigates a phenomenon in the real-world context (16), e.g. the cognitive process or experience of patients and healthcare professionals with disease, medicines use and risk minimisation measures, including related media behaviours, communication needs and preferences (17);
- Grounded theory study: aims at developing concepts that are grounded in the data and subsequently formulates - through an iterative and comparative process - a well-grounded theory on a cognitive process or experience, e.g. to explore existing knowledge and beliefs in context of health communication (6,18–20);
- Mixed methods study: combines qualitative with quantitative methods to benefit from the strengths of each, typically using multiple data sources, perspectives and data analysis methods in an approach called triangulation (5–7);

- Case study: intends to gain an in-depth understanding of a unique event in its complexity, applying qualitative, quantitative or mixed methods data and analysis, e.g. of stakeholder input in a public hearing (21,22);
- Action research study: evaluates ongoing implementation of an action in a participatory approach (6,23), e.g. the implementation of a RMM in healthcare with active research participation of patients and healthcare professionals.

Qualitative studies should be designed for rigour, and tools for assessing their quality are encouraged to be used, in order for the studies to serve as evidence for evaluation and decision-making on RMM (9,14,24,25).

XVI. ADD.II.3.2. Survey methods

The design and conduct of a survey study should be considered carefully with a view to minimise potential bias and optimise the generalisability of the results in the target population.

Sampling and recruitment of survey participants should ensure that the study population is similar and hence representative of the target population and avoid selection bias due to dissimilarity in one or several relevant aspects. For example, where marketing authorisation applicants/holders rely on prescribing physicians to recruit patients, effort should be made to mitigate the potential for selection bias.

Bias may be minimised by selecting the optimal sampling frame, accounting for the expected response rate, age, sex, geographical distribution and additional characteristics of the study population, and by achieving similar response rates across diverse participants to avoid non-response bias. Bias may also be minimised by assuring that the sample contains appropriate diversity to allow stratification of results by key population characteristics (e.g. by oversampling a small but important subgroup). For example, in a physician survey, the sampling strategy should consider whether a general random sample would be sufficient, or if the sampling frame should be stratified by key characteristics such as specialty, type of practice (e.g. general practitioner, specialist or hospital care). In a patient survey, characteristics such as socio-economic status and education, medical condition(s), chronic versus acute medicines use should be considered for optimising the sampling frame.

The recruitment strategy should also account for chances of achieving accurate and complete data collection. Efforts should be made to document the proportion of non-responders and their

characteristics to evaluate potential effects on the representativeness of the sample.

The data collection instrument should be designed so that it avoids desired-response-bias (e.g. obvious multiple-choice response), covers all relevant aspects of the RMM and is able to identify different levels of risk knowledge and attitude. For a data collection instrument to be considered reliable the following principles should be adhered:

- Pre-testing and validation: Testing the draft instrument on samples of subjects should be similar to the study population to identify questions that are poorly understood, ambiguous, or produce invalid responses. Pre-tests should be carried out using the same procedures that will be used when applying the data collection instrument to the study population.
- Content validity: Items or variables in the data collection instrument should capture all aspects related to end-users' risk knowledge and attitudes on the RMM tool. It is also important that the items or variables included in the data collection instrument are clear and unambiguous and that questions pertaining directly to the implemented regulatory action are avoided (e.g. "do you know that product X is contraindicated for disease Y?").
- Construct validity: Items or variables in the in the data collection instrument should be developed in a way that they are likely to accurately measure (at different degrees) end-users' risk knowledge and attitudes on the RMM tool.

The following analytical elements should be considered for quantitative surveys exploring risk knowledge:

- Descriptive statistics, such as:
  - Response rate (i.e. proportion of participants who responded of the total number of invited participants);
  - Rate of incomplete responses among responding participants;
  - Pooled proportion of participants responding correctly to the proposed questions;
  - Stratification by selected characteristics such as target population (e.g. healthcare professional or specialist, patient, caregiver), geographic region, receipt and type of RMM tool;
- Comparison of responder and non-responder characteristics (if data is available);
- Comparison of responders and overall target population characteristics;
- Comparison of characteristics of responders with correct and incorrect answers.

In order to obtain valid survey results, a weight may have to be attached to each respondent considering the following:

- Differences in selection, e.g. if certain subgroups were over-sampled;
- Differences in response rates between sub-groups;
- Differences of responders compared to target population (e.g. speciality, volume of prescribing);
- Clustering.

Although survey studies aimed at evaluating risk knowledge and attitudes do not attempt to collect patient health-related information, patients who complete the survey are likely to have received the medicinal product revealing the condition/disease they suffer from. Therefore, unless the patient response is completely anonymous, regulations to protect patient health information apply and informed consent must be provided. Survey studies should ensure the protection of individuals with regard to the processing of personal data.

XVI. ADD.II.3.3. Methods evaluating behaviour and health outcomes

Outcomes of risk minimisation may be monitored and evaluated with non-interventional methods that measure how medicinal products are prescribed, dispensed or used over time, by means of electronic health records, medical chart abstraction or claims data (see XVI.Add.II.2.1.). Detecting changes in adverse reaction reporting, despite known limitations, may contribute to this monitoring (see XVI.Add.II.2.1.7.). Outcomes of interest and evaluation objectives (see GVP Module XVI) may not be limited to the medicinal product or product class targeted by the regulatory action (see Figure XVI.Add.II.1.).

Where feasible, a control group unexposed to the RMM should be included to ascertain if the observed outcome is attributable to the RMM intervention or to the presence of external factors (e.g. secular trends). Since RMM are generally implemented in the entire target population, the identification of a control group may not always be possible and the comparison against suitable reference values should be considered (see GVP Module XVI).

For marketed medicinal products, quantitative measures (see GVP Module XVI) should be estimated in the same study population before and after the RMM intervention, with pre-intervention information acting as a surrogate control (i.e. quasi-experimental designs). However, in absence of pre-intervention information (e.g. for medicinal products with RMM at the time of

initial marketing authorisation), any effect of the RMM can be only estimated against a predefined reference value (i.e. literature review, historical data, expected frequency in general population, outcome frequency in the pre-authorisation clinical trials) taking into account all possible limitations (26) (see GVP Module XVI). The selection of a reference value should be justified.

Whilst appropriate to describe the population for understanding generalisability of observed outcomes, simple descriptive approaches do not determine whether statistically significant changes have occurred (3,27).

XVI. ADD.II.3.3.1. Single time point cross-sectional study

The guidance on cross-sectional study designs in GVP Module VIII applies. Cross-sectional studies can only measure temporal associations at a single point in time. Therefore, the method is commonly used to monitor indicators of RMM implementation and to complement other studies on e.g. patterns of medicines use.

XVI. ADD.II.3.3.2. Before/after cross-sectional study

A before/after cross-sectional study is defined as an evaluation at one point in time before and one point in time after the date of the RMM intervention (accounting for the implementation timeframe). When uncontrolled, baseline trends are ignored, potentially leading to RMM outcomes being estimated incorrectly. Including a control can strengthen this design (3). Careful consideration should be given to whether a suitable control can be identified, for example healthcare professionals not targeted by the RMM to control for general prescribing trends.

When RMM is put in place at the time of initial marketing authorisation, the comparison of an outcome frequency indicator obtained post-RMM intervention against a predefined reference value would be acceptable (see GVP Module XVI).

XVI. ADD.II.3.3.3. Before/after time series analysis

Time series analysis has commonly been used to evaluate the effectiveness of regulatory actions and should be considered whenever feasible as one of the more robust approaches (3). A time series analysis spanning the date of a regulatory action (e.g. interrupted segmented regression analysis) accounts for secular trends and can provide statistical evidence about whether observed changes are significant.

Time series analysis is well suited to study changes in outcomes that are expected to occur

relatively quickly following a regulatory action, such as prescribing rates. Time series analysis can be used to estimate the immediate change in outcome after the regulatory action, the change in trend in the outcome over time compared to before, and the effects at specific time points following the regulatory action. Cochrane Effective Practice and Organisation of Care (EPOC) provides further information on the utility of time series regression (28).

Time series analysis requires that enough data points are collected before and after the RMM intervention. The power to undertake a time series analysis depends upon the sample size, the effect size, the prevalence of exposure, the number of data points and their balance before and after the intervention time period (29). Long time periods may also be affected by changes in trends unrelated to the RMM that can violate model assumptions and introduce confounding when evaluating RMM.

Like the before-after cross-sectional design, including a control can strengthen this design by minimising potential confounding.

Factors such as autocorrelation, seasonality and non-stationarity should be checked when conducting time series analysis and may require more complicated modelling approaches if detected or considered likely to occur (30). Interventions associated with major immediate changes (e.g. product withdrawals) may be evaluated without regression modelling, but they risk producing spurious results when the changes are more subtle or multiple confounders are present (3).

Time series analysis also requires that the time point of RMM intervention (accounting for the implementation timeframe) is known prior to the analysis. When this is not the case (e.g. during a phased roll out of a regulatory action) more complex modelling techniques and data-driven time series approaches (e.g. Joinpoint analysis) could be considered (31). There are literature examples of time series analysis using a control (32), estimating effects 12 months after the regulatory action (27), dealing with autocorrelation and seasonality (33), and using Joinpoint regression (34).

XVI. ADD.II.3.3.4. Cohort study

The cohort study design as defined in GVP Module VIII may be useful to establish the base population for the conduct of drug utilisation studies to assess behavioural changes and health outcomes (see GVP Module XVI) or to perform aetiological studies (see GVP Module VIII). Modelling the effect of regulatory actions on health outcomes may require more complex study designs.

Cohort studies are in particular suitable to examine pregnancy prevention programmes (35), medicines use in RMM targeted populations (36) and effects on health outcomes.

In aetiological studies, propensity score methodology may be used, e.g. to measure the reduction in stroke with warnings on the use of antipsychotics (37).

XVI. ADD.II.3.3.5. Randomised trial

A randomised trial may be suitable to evaluate the effectiveness of components of regulatory actions, in particular safety information and dissemination channels. Test groups should be representative of the target population. Stepped wedge cluster trial designs may be considered for a phased role out of the intervention (38). Only a few examples of effectiveness evaluation with this study design exist in line with GVP Module VIII (3).

XVI. ADD.II.4. Checklist for harmonised reporting of study results

Intended for pharmaceutical risk Minimization Evaluation Studies" (i.e. the "RIMES Statement"), tailored to the study designs frequently used for risk minimisation evaluation (39), can be used to standardise and improve the reporting from such studies. Reporting items have been derived from the RIMES Statement for reporting results of effectiveness studies (see Table XVI.App.II.1.), to facilitate the completion of the final report of an RMM effectiveness study in the format for PASS reports described in GVP Module VIII.

Table XVI.ADD.II.1.: Additional PASS reporting items for effectiveness study reports

PASS report section	Additional reporting items
6. Rationale and background	Design of the regulatory action and its implementation in terms of: - Goals and objectives of the action; - Implementation timetable; - Underlying dissemination- and implementation-relevant theory(ies), including the expected causal pathway for effectiveness; - Targeted recipient(s), population/healthcare setting, including key characteristics (e.g. geography, disease condition, age, sex, ethnicity, socioeconomic status, medical speciality);

	- Regulatory action/communication/RMM tool selection and development, including pilot testing and formative evaluation; - Consideration of cultural issues and sensitivity and adaptation (e.g. local language, sociocultural values and traditions); - Stakeholder engagement (e.g. from patient and healthcare professional representatives); - Message content; - Dissemination modality, including rationale for why specific modality(ies) were selected; - Success metrics with a priori specification of measures and threshold for determination of intervention success; - Organisations responsible for implementing the regulatory action at the level of authorities and healthcare; - Selection of implementers including their qualifications and training for implementation; - Ecological context of the healthcare settings (e.g. number, type and location(s)); - Fidelity to a formal protocol for implementing the regulatory action and important intentional modifications made to regulatory action or its implementation after commencement, including at local level
11.4 Generalisability	Discussion of whether the results demonstrate the intended effect across the targeted diverse recipient(s), population/ healthcare setting
12. Other information	Likelihood of sustainability and discussion of the degree to which the regulatory action was integrated into the delivery setting (e.g. policies or incentives put in place to support implementation maintenance)

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