

Guideline on Good Pharmacovigilance Practices (GVP)

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Drug Sector

Saudi Food & Drug Authority

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Drug Sector

Vision and Mission

Vision

To be the leading regional Drug Regulatory Authority for pharmaceuticals and cosmetic products, with professional excellence and services that contribute to the protection and advancement of public health in the Kingdom of Saudi Arabia.

الرؤية

أن يكون قطاع الدواء رائداً إقليمياً في الرقابة على الأدوية ومستحضرات التجميل، ويقدم خدماته بمهنية متميزة تساهم في حماية وتعزيز الصحة في المملكة العربية السعودية.

Mission

Protecting public health by ensuring safety, quality, efficacy and accessibility of human, veterinary drugs and biological products, and safety of cosmetics, through administration of a national regulatory system which is consistent with international best practice. Through our mission, we also provide accurate and scientific-based information to the public and healthcare professionals.

الرسالة

حماية الصحة العامة من خلال ضمان أمان وجودة وفعالية وتوفير الأدوية البشرية والبيطرية والمنتجات الحيوية وسلامة مواد التجميل عبر تطبيق نظام وطني للرقابة متوافق مع أفضل الممارسات الدولية وتقديم المعلومات الدوائية المبنية على أسس علمية للعامة والمهنيين الصحيين.

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**The requirements explained in this guideline is based mainly
on the European Good Pharmacovigilance Practices (GVP)
guideline**

Please visit SFDA's website at

[http://www.sfda.gov.sa/en/drug/drug_reg/Regulations/GVP-
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for the GVP- Definition

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Module I – Pharmacovigilance systems and their quality systems

1.A Introduction

This Module contains guidance for the establishment and maintenance of quality assured pharmacovigilance systems for marketing authorisation holders. How the systems of these organisations 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 marketing authorisation holder and by The Saudi Food and Drug Authority (SFDA) to fulfill the tasks and responsibilities listed in this guideline and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance. The SFDA likewise maintains a pharmacovigilance system to fulfil its pharmacovigilance activities.

For performing their pharmacovigilance activities, marketing authorisation holders, 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 referenced in the way explained in the GVP Introductory Cover Note and 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 organisation to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

A pharmacovigilance system, like any system, is characterised 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 organisational 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 of the following activities:

- quality planning: establishing structures and planning integrated and consistent processes;
- quality adherence: carrying out tasks and responsibilities in accordance with quality requirements;
- quality control and assurance: monitoring and evaluating how effectively the structures and processes have been established and how effectively the processes are being carried out; 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 authorised medicinal products within or outside the terms of marketing authorisation 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 organisation should be involved in and support the pharmacovigilance system on the basis of task ownership and responsibility in a degree according to their tasks and assigned responsibilities.
- All persons involved with the entire organisation should engage in continuous quality improvement following the quality cycle in I.B.3..
- Resources and tasks should be organised as structures and processes in a manner that will support the proactive, risk-proportionate, continuous and integrated conduct of pharmacovigilance.
- All available evidence on the risk-benefit balance of medicinal products should be sought and all relevant aspects, which could impact on the risk-benefit balance and the use of a product, should be considered for decision-making.
- Good cooperation should be fostered between marketing authorisation holders, the SFDA, public health organisations, 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 organisation should be responsible for:

- ensuring that the organisation 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 organisation;
- identifying and investigating concerns arising within an organisation regarding suspected non-adherence to the requirements of the quality and pharmacovigilance systems and taking corrective, preventive and escalation action as necessary;
- ensuring that audits are performed (see I.B.12.).

In relation to the management responsibilities described above, upper management within an organisation 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 organisation; and
- assigning roles, responsibilities and authorities to staff members according to their competencies and communicating and implementing these throughout the organisation.

I.B.7. Training of personnel for pharmacovigilance

Achieving the required quality for the conduct of pharmacovigilance processes and their outcomes by an organisation 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 marketing authorisation holders, this training shall relate to the roles and responsibilities of the personnel.

The organisation 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 organisation 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 organisation 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 organisations as well as the individual staff members.

Adequate training should also be considered by the organisation 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 organisation 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 Marketing Authorisation Holders

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

- the continuous monitoring of pharmacovigilance data, the examination of options for risk minimisation and prevention and that appropriate measures are taken by the marketing authorisation holder (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 authorisation 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 marketing authorisation holder with the SFDA, including communication on new or changed risks (see Module XII and XV- which will be released), the pharmacovigilance system master file (see Module II), risk management systems (see Module V), risk minimisations measures (see Modules V and XVI), periodic safety update reports (see Module VII), corrective and preventive actions (see Modules II, III and IV) and post-authorisation safety studies (see Module VIII);
- the update of product information by the marketing authorisation holder in the light of scientific knowledge (see Module XII which will be realised);
- appropriate communication of relevant safety information to healthcare professionals and patients (see Module XII and XV which will be realised)

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, marketing authorisation holders and the general public;
- conducting inspections, including pre-authorisation 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 organisation 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, marketing authorisation holders 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 authorised 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 carry out a process and may take the format of a standard operating procedure and other work instruction or quality manual. A quality manual documents the scope of the quality system, the processes of the quality system and the interaction between the two. A quality record is a document stating results achieved or providing evidence of activities performed.

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

- quality objectives specific to their organisations 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 organisational 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 marketing authorisation holders

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

- their human resource management in the pharmacovigilance system master file (PSMF) (see Module II)
- job descriptions defining the duties of the managerial and supervisory staff.
- an organisational chart defining the hierarchical relationships of managerial and supervisory staff
- instructions on critical processes (see I.B.11.3.) in the pharmacovigilance system master file (PSMF) (see Module II); and
- their record management system in the pharmacovigilance system master file (PSMF) (see Module II).

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

For the requirements of documenting the quality system in the pharmacovigilance system master file (PSMF) or its annexes, see 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 authorised medicinal products;
- establishing, assessing and implementing risk management systems and evaluating the effectiveness of risk minimisation;

- collection, processing, management, quality control, follow-up for missing information, coding, classification, duplicate detection, evaluation and timely electronic transmission of individual case safety reports (ICSRs) from any source;
- signal management;
- scheduling, preparation (including data evaluation and quality control), submission and assessment of periodic safety update reports;
- meeting commitments and responding to requests from the SFDA, including provision of correct and complete information;
- interaction between the pharmacovigilance and product quality defect systems;
- communication about safety concerns between marketing authorisation holders and the SFDA, in particular notifying changes to the risk-benefit balance of medicinal products;
- communicating information to patients and healthcare professionals about changes to the risk-benefit balance of products for the aim of safe and effective use of 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 authorisations 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 organisation'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 organisation, amongst organisations sharing pharmacovigilance tasks as well as between marketing authorisation holders 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 minimising risks and supporting their safe and effective use in patients.

The organisation 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 programmes 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 marketing authorisation holder, a report shall be drawn up on the results for each quality audit and any follow-up audits be sent to the management responsible for the matters audited. The report should include the results of audits of organisations or persons the marketing authorisation holder has delegated tasks to, as these are part of the marketing authorisation holder'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 minimising 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 marketing authorisation holder in KSA

The marketing authorisation holder in KSA is responsible for the respective pharmacovigilance tasks and responsibilities in order to assure responsibility and liability for its authorised medicinal products and to ensure that appropriate action can be taken, when necessary.

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

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

A description of the pharmacovigilance system shall be developed by the applicant for a marketing authorisation in the format of a pharmacovigilance system master file (PSMF) and be maintained by the marketing authorisation holder for all authorised medicinal products (see Module II). The applicant or the marketing authorisation holder is also responsible for developing and maintaining product-specific risk management systems (see Module V).

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

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

As part of the pharmacovigilance system, the marketing authorisation holder shall have permanently and continuously at its disposal A full-time qualified person responsible for pharmacovigilance (QPPV) reside in KSA.

The marketing authorisation holder shall submit the name and contact details of the QPPV to the SFDA. Changes to this information should be submitted in accordance with regulation on the SFDA variations guidelines.

The duties of the QPPV shall be defined in a job description. The hierarchical relationship of the QPPV shall be defined in an organisational chart together with those of other managerial and supervisory staff.

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

Each Pharmacovigilance system can have only one QPPV. A QPPV may be employed by more than one marketing authorisation holder and this should be approved by the SFDA, for a shared or for separate pharmacovigilance systems or may fulfil the role of QPPV for more than one pharmacovigilance system of the same marketing authorisation holder, provided that the QPPV is able to fulfil all obligations.

Reporting in this context relates to pharmacovigilance tasks and responsibilities and not necessarily to line management. A contact person at national level may also be nominated as the QPPV.

The marketing authorisation holder shall ensure that the QPPV has sufficient authority to influence the performance of the quality system and the pharmacovigilance activities of the marketing authorisation holder. The marketing authorisation holder should therefore ensure that the QPPV has access to the pharmacovigilance system master file (PSMF) as well as authority over it and is notified of any changes to it in accordance with Module II (see I.C.1.3). The authority over the pharmacovigilance system and the PSMF should allow the QPPV to implement changes to the system and to provide input into risk management plans (see Module V) as well as into the preparation of regulatory action in response to emerging safety concerns (see Module XII, which will be realised).

Overall, the marketing authorisation holder should ensure that structures and processes are in place, so that the QPPV can fulfil the responsibilities listed in I.C.1.3.. In order to do this, the marketing authorisation holder should ensure that mechanisms are in place so that the QPPV receives all relevant information and that the QPPV can access all information the QPPV considers relevant, in particular on:

- emerging safety concerns and any other information relating to the benefit-risk evaluation of the medicinal products covered by the pharmacovigilance system;

- ongoing or completed clinical trials and other studies the marketing authorisation holder is aware of and which may be relevant to the safety of the medicinal products;
- information from sources other than from the specific marketing authorisation holder, e.g. from those with whom the marketing authorisation holder has contractual arrangements; and
- the procedures relevant to pharmacovigilance which the marketing authorisation holder has in place at every level in order to ensure consistency and compliance across the organisation.

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. Such information may also be used to provide assurance to the QPPV that commitments in the framework of risk management plans and post-authorisation safety systems are being adhered to.

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

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

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

When a marketing authorisation holder intends to establish a partnership with another marketing authorisation holder, organisation or person that has a direct or indirect impact on the pharmacovigilance system, the QPPV should be informed early enough and be involved in the preparation of the corresponding contractual arrangements (see I.C.1.5.) so that 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 marketing authorisation holder shall ensure that the QPPV has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities. The QPPVs should have a minimum of bachelor degree of pharmacy or medicine, basic training in epidemiology and biostatistics and should be licensed by Saudi Commission for Health Specialties. In addition. They 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 marketing authorisation holder will assess the qualification of the QPPV prior to appointment by, for example, reviewing university qualifications, knowledge of KSA pharmacovigilance requirements and experience in pharmacovigilance.

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

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

The QPPV appointed by the marketing authorisation holder shall be appropriately qualified (see I.C.1.2.) and shall be at the marketing authorisation holder's disposal permanently and continuously (see I.C.1.1.). Back-up procedures in the case of absence of the QPPV shall be in place and should be accessible through the QPPV's contact details. The QPPV should ensure that the back-up person has all necessary information to fulfil the role.

The QPPV shall be responsible for the establishment and maintenance of the marketing authorisation holder's pharmacovigilance system and therefore shall have sufficient authority to influence the performance of the quality system and the pharmacovigilance activities and to promote, maintain and improve compliance with the legal requirements. Hence, the QPPV should have access to the pharmacovigilance system master file (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:

- 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 authorisations and other commitments relating to safety or the safe use of the products;
- having awareness of risk minimisation measures;
- being aware of and having sufficient authority over the content of risk management plans;

- being involved in the review and sign-off of protocols of post-authorisation safety studies conducted in KSA or pursuant to a risk management plan agreed in KSA;
- having awareness of post-authorisation 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 also as a contact point for pharmacovigilance inspections.

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

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

I.C.1.4. Specific quality system processes of the marketing authorisation holder in KSA

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

- the submission of adverse reaction data to National Pharmacovigilance and Drug Safety Center (NPC) within the legal timelines;
- the monitoring of the use of terminology referred to in either systematically or by regular random evaluation;
- the retention of minimum elements of the pharmacovigilance system master file (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 marketing authorisation holder;
- the retention of pharmacovigilance data and documents relating to individual authorised medicinal products as long as the marketing authorisation exists and for at least further 10 years after the marketing authorisation has ceased to exist;
- that the product information is kept up-to-date by the marketing authorisation holder 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 marketing authorisation holder is taken over by another organisation should be complete.

I.C.1.5. Quality system requirements for pharmacovigilance tasks subcontracted by the marketing authorisation holder

The marketing authorisation holder may subcontract certain activities of the pharmacovigilance system to third parties, i.e. to another organisation or person (where the same requirements apply to a person as for an organisation). This may include the role of the QPPV. The marketing authorisation 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 authorisation holder. It should be noted that subcontracting any pharmacovigilance activities must be pre-authorized by the SFDA and restricted to certain circumstances.

Where a marketing authorisation 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 organisation to which the tasks have been subcontracted.

When subcontracting tasks to another organisation, the marketing authorisation holder shall draw up subcontracts and these should be detailed, up-to-date and clearly document the contractual arrangements between the marketing authorisation holder and the other organisation, describing arrangements for delegation and the responsibilities of each party. A description of the subcontracted 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 certain pharmacovigilance activities, will be subject to pre-authorisation 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 authorisation 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 organisation by the marketing authorisation holder or introduction of other methods of control and assessment are recommended.

For responsibilities of the marketing authorisation 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 authorised 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 from Saudi vigilance, and all other sources.
2. Investigation of adverse reactions.
3. Regularly review Drug monitor of safety concerns.
4. Discussion of emerging safety concerns at the request of the NPC.
5. Discussion of PSURs at the request of the NPC.
6. Recommendations to the NPC on Risk-benefit evaluations and actions necessary to minimize risk and maximize benefit.
7. Providing advice to the NPC 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 referred 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 authorised medicinal products are retained as long as the marketing authorisation exists or for at least further 10 years after the marketing authorisation 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 organisational structures and the distribution of tasks and responsibilities as well as establish contact points, in particular to facilitate interaction between the SFDA, marketing authorisation holders 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 marketing authorisation holders, 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 recognised 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 marketing authorisation holders and the public. The SFDA publishes its notifications on the SFDA website.

Module II – Pharmacovigilance System Master File

II.A. Introduction

The pharmacovigilance system master file defined as a detailed description of the pharmacovigilance system used by the marketing authorisation holder with respect to one or more authorised 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 pharmacovigilance system master file shall be located either at the site in the KSA where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the KSA where the qualified person responsible for pharmacovigilance operates

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

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

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

IIB. Structures and processes

The pharmacovigilance system master file is a legal requirement in the KSA. This guidance concerns the requirements for the pharmacovigilance system master file and is applicable for any medicinal product authorised in the KSA, irrespective of the marketing authorisation procedure. The required content and management of the pharmacovigilance system master file applies irrespective of the organisational structure of a marketing authorisation holder, including any subcontracting or delegation of activities, or their location. Irrespective of the location of other activities, the qualified person for pharmacovigilance (QPPV's) residence, the location at which he/she carries out his/her tasks and the pharmacovigilance system master file location must be within the KSA.

The content of the pharmacovigilance system master file should reflect global availability of safety information for medicinal products authorised in the KSA, with information on the pharmacovigilance system not just confined to local or regional activities.

II.B.1. Objectives

The pharmacovigilance system master file 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 authorisations holder(s), the fulfilment of supervisory responsibilities of the QPPV, and of inspections or other verification of compliance by SFDA. The pharmacovigilance system master file provides an overview of the pharmacovigilance system, which may be requested and assessed by SFDA during marketing authorisation application(s) or post-authorisation.

Through the production and maintenance of the pharmacovigilance system master file, the marketing authorisation holder 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

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

The requirement for submission of a detailed description of the pharmacovigilance system (DDPS) with each marketing authorisation application is no longer applicable. For new applications, the summary of the pharmacovigilance system must be included in the application.

Amendments to the particulars or documents referred to in the summary of the applicant's pharmacovigilance system.

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 prepare and maintain a pharmacovigilance system master file. In all circumstances, an appropriate pharmacovigilance system must be in place, described in a PSMF, with the location and QPPV details entered and maintained.

II.B.2.2. Location

The pharmacovigilance system master file shall be located within the KSA, either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates, irrespective of the format (paper-based or electronic format file).

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 marketing authorisation holder or a contracted third party. Where the pharmacovigilance system master file 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 pharmacovigilance system master file

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 marketing authorisation holder fulfils their responsibilities. Since a specific QPPV has responsibility for the pharmacovigilance system, changes to the pharmacovigilance system master file should also be notified to the QPPV in order to support their authority to make improvements to the system. The types of changes that should be routinely and promptly notified to the QPPV are:

- Updates to the pharmacovigilance system master file or its location that are notified to the SFDA;
- The addition of corrective and/or preventative actions to the pharmacovigilance system master file (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 pharmacovigilance system master file to the SFDA;
- Transfer of significant services for pharmacovigilance to a third party (e.g. outsourcing of PSUR production);
- Inclusion of products into the pharmacovigilance system for which the QPPV is responsible;
- Changes for existing products which may require a change or increased workload in relation to pharmacovigilance activity e.g. new indications, studies.

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

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

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

authorisation holder. In either case, a single and specific pharmacovigilance system master file shall be in place to describe each system.

- A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file.
- Where a pharmacovigilance system is shared by several marketing authorisation holders each marketing authorisation holder is responsible ensuring that a pharmacovigilance system master file exists to describe the pharmacovigilance system applicable for his products, and this should be approved by the SFDA. For a particular product(s) the marketing authorisation holder may delegate through written agreement (e.g. to a licensing partner or contractor) part or all of the pharmacovigilance activity for which the marketing authorisation holder is responsible. In this case the pharmacovigilance system master file of the marketing authorisation holder may cross refer to all or part of the pharmacovigilance system master file managed by the system of the party to whom the activity has been delegated subject to agreement on access to that system's information for the marketing authorisation holder and the SFDA. The marketing authorisation holder 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 pharmacovigilance system master file in a current and accessible state can be delegated.
- Where applicable, a list of all pharmacovigilance system master files held by the same marketing authorisation holder 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 pharmacovigilance system master file. The address of the location of the pharmacovigilance system master file 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 marketing authorisation holder retains ultimate responsibility for the

pharmacovigilance system, submission of information about the pharmacovigilance system master file location, maintenance of the pharmacovigilance system master file and its provision to the SFDA upon request. Detailed written agreements describing the roles and responsibilities for pharmacovigilance system master file content, submissions and management, as well as to govern the conduct of pharmacovigilance in accordance with the legal requirements, 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 pharmacovigilance system master files. Accessibility of the pharmacovigilance system master file to all the applicable marketing authorisation holder(s), and its provision to the SFDA should be defined in written agreements. It is vital that marketing authorisation holder(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 pharmacovigilance system master file

The pharmacovigilance system master file shall include documents to describe the pharmacovigilance system. The content of the pharmacovigilance system master file should reflect the global availability of safety information for medicinal products authorised 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 pharmacovigilance system master file is that the primary topic sections contain information that is fundamental to the description of pharmacovigilance system. Detailed information is required to fully describe the system, and, since this may change frequently, it 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 authorisation (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 QPPV, contact details shall be provided in the marketing authorisation 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 qualified person responsible for pharmacovigilance, including proof of registration with the National Pharmacovigilance and Drug Safety Center (NPC);
- contact details;
- details of back-up arrangements to apply in the absence of the qualified person responsible for pharmacovigilance; and

A list of tasks that have been delegated by the qualified person for pharmacovigilance 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, telephone, fax and e-mail and represent the usual working address of the QPPV, which may therefore be different to a marketing authorisation holder address. If the QPPV is employed by a third party, even if the usual working address is an office of the marketing

authorisation holder, this should be indicated and the name of the company the QPPV works for provided.

II.B.4.2. PSMF section on the organisational structure of the marketing authorisation holder

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

- The organisational structure of the marketing authorisation holder(s), showing the position of the QPPV in the organisation.
- The site(s) where the pharmacovigilance functions are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production, signal detection and analysis, risk management plan management, pre- and post-authorisation 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 pharmacovigilance system master file, 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 and if applicable, to the pharmacovigilance system applied to products authorised in the Community.

Links with other organisations, 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 organised according to; service providers (e.g. medical information, auditors, patient support programme 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.

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 authorised 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 pharmacovigilance system master file. Information about third parties (licence 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 programmes sponsored by the marketing authorisation holder 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 harmonisation, it is recommended that the list should be comprehensive for products authorised 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/programme, the applicable country(ies), the product(s) and the main objective. It should distinguish between interventional and non-interventional studies and should be organised per active substance. The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes completed in the last two years and may be located in an Annex or provided separately.

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

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

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

Continuous monitoring of product risk-benefit profile(s) applied and the result of evaluation and the decision making process for taking appropriate measures; this 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 minimisation 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 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 marketing authorisation holder 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 minimisation and prevention and appropriate measures are taken by the marketing authorisation holder;
2. the scientific evaluation by the marketing authorisation holder of all information on the risks of medicinal products;
3. the submission of accurate and verifiable data on serious and non-serious adverse reactions to the national medicines 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 marketing authorisation holder with the national medicines authorities, including communication on new risks or changed risks, the pharmacovigilance system master file, risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions, and post-authorisation studies;
6. the update of product information by the marketing authorisation holder in the light of scientific knowledge, and on the basis of a continuous monitoring by the marketing authorisation holder of information released by the national medicines authorities;
7. appropriate communication by the marketing authorisation holder of relevant safety

information to healthcare professionals and patients.

These interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to 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 pharmacovigilance system master file should contain evidence of the ongoing monitoring of performance of the pharmacovigilance system including compliance of the main outputs of pharmacovigilance. The pharmacovigilance system master file 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, PSURs or other submissions;
- An overview of the timeliness of PSUR reporting to the SFDA (the annex should reflect the latest figures used by the marketing authorisation holder 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 risk management plan commitments, or other obligations or conditions of marketing authorisation(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 pharmacovigilance system master file, 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 organisation 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 pharmacovigilance system master file 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 organisational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organisational 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 organisation 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 organisation 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 pharmacovigilance system master file. 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 pharmacovigilance system master file shall also contain a note associated with any audit where significant findings are raised. This means that the presence of findings that fulfil the 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 pharmacovigilance system master file it is sufficient to provide a brief description of the corrective and/or preventative action(s) associated with the significant finding, the date it was identified and the anticipated resolution date(s), with cross reference to the audit report and the documented corrective and preventative action plan(s). In the annex, in the list of audits conducted, those associated with unresolved notes in the pharmacovigilance system master file, should be identified. The note and associated corrective and preventative action(s), shall be documented in the pharmacovigilance system master file until the corrective and/or preventative action(s) have been fully implemented, that is, the note is only removed once corrective action and/or sufficient improvement can be demonstrated or has been independently verified. The addition, amendment or removal of the notes must therefore be recorded in the logbook.

As a means of managing the pharmacovigilance system, and providing a basis for audit or inspection, the pharmacovigilance system master file 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 pharmacovigilance system master file shall contain the following documents:

- A list of medicinal products covered by the pharmacovigilance system master file including the name of the medicinal product, the name of the active substance(s).

The list should be organised per active substance and, where applicable, should indicate what type of product specific safety monitoring requirements exist (for example risk minimisation measures contained in the risk management plan or laid down as conditions of the marketing authorisation, non-standard PSUR periodicity). The monitoring information may be provided as a secondary list.

For marketing authorisations 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 pharmacovigilance system master file(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 pharmacovigilance system master files.

- Where pharmacovigilance systems are shared, all products that utilise 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, organised 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 pharmacovigilance system master files held by the same marketing authorisation holder. This list should include the pharmacovigilance system master file 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 marketing authorisation holder shall record in the logbook any alteration of the content of the pharmacovigilance system master file made within the last five years. Also, the marketing authorisation holder 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 marketing authorisation holders to implement change control systems and to have robust processes in place to continuously be informed of relevant changes in order to maintain the pharmacovigilance system master file accordingly. 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;
- Organisational changes, such as takeovers, mergers, the sites at which pharmacovigilance is conducted or the delegation/transfer of pharmacovigilance system master file management.

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

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

Marketing authorisation holders should be able to justify their approach and have document control procedures in place to govern the maintenance of the pharmacovigilance system

master file. As a basis for audit and inspections, the pharmacovigilance system master file provides a description of the pharmacovigilance system at the current time, but the functioning and scope of the pharmacovigilance system in the past may need to be understood.

Changes to the pharmacovigilance system master file 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 pharmacovigilance system master file should be retained in a manner that ensures its legibility and accessibility.

II.B.6. Pharmacovigilance system master file presentation

The pharmacovigilance system master file 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, marketing authorisation holders should be aware that immediate access to the pharmacovigilance system master file may also be required by the SFDA, at the stated pharmacovigilance system master file location or QPPV site (if different).

II.B.6.1. Format and layout

The pharmacovigilance system master file 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 pharmacovigilance system master file 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 pharmacovigilance system master

file in order to ensure appropriate control over the content and to assign specific responsibilities for the management of pharmacovigilance system master file in terms of change control and archiving.

The pharmacovigilance system master file 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 pharmacovigilance system master file 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 QPPV third party company name (if applicable).
- The name of other concerned MAH(s) (sharing the pharmacovigilance system)
- The list of pharmacovigilance system master files for the MAH (concerning products with a different pharmacovigilance system)
- The date of preparation / last update

The headings used in II.B.4 should be used for the main content of the pharmacovigilance system master file. 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 Qualified Person responsible for pharmacovigilance, 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 Organisational 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

Computerised 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 pharmacovigilance system master file, 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 computerised systems and databases is used, Annex D should simply be described as ‘unused’ in the indexing, in order that recipients of the pharmacovigilance system master file are assured that missing content is intended.

II.C. Operation within the KSA

II.C.1. Responsibilities

II.C.1.1. Marketing authorisation holders and applicants

Marketing authorisation holders 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 pharmacovigilance system master file that records the pharmacovigilance system in place with regard to one or more authorised products. A single QPPV shall be appointed to be responsible for the establishment and maintenance of the pharmacovigilance system described in the pharmacovigilance system master file.

Applicants are required, at the time of initial marketing authorisation 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 authorisation and placing of the product on the market. During the evaluation of a marketing authorisation application the applicant may be requested to provide a copy of the pharmacovigilance system master file for review.

The applicant/marketing authorisation holder is responsible for establishing the pharmacovigilance system master file in the KSA (at any marketing authorisation holder 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 authorisation application (as applicable). The pharmacovigilance system master file shall describe the pharmacovigilance system in place at the current time. Information about elements of the system to be implemented in future may be included, but these should be clearly described as planned rather than established or current.

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

When the QPPV and related contact details change or when the location of the pharmacovigilance system master file changes, the marketing authorisation holder is required to submit the appropriate variation application(s) to the SFDA, as applicable. Marketing authorisation holders will also be responsible for notifying the SFDA immediately of any change in the QPPV details and the pharmacovigilance system master file address details so that the NPC database referred to.

II.C.2. Accessibility of the pharmacovigilance system master file

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

The marketing authorisation holder shall maintain and make available on request a copy of the pharmacovigilance system master file. The marketing authorisation holder must submit

the copy 7 days at the latest after receipt of the request from the SFDA. The pharmacovigilance system master file should be submitted in a readable electronic format or clearly arranged printed copy.

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

The pharmacovigilance system master file should not routinely be requested during the assessment of new marketing authorisation applications (i.e. pre-authorisation), 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 pharmacovigilance system master file should reflect **global** availability of safety information for medicinal products authorised 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. apply.

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

Remember 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 authorisation 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;

check list 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 is accepted by the SFDA **that for only a transitional period** the QPPV qualifications may be expressed in terms of his pharmacovigilance training rather than his practical experience in pharmacovigilance. Under these circumstances, once the QPPV is appointed, the MAH is responsible of providing him the unachieved trainings in light of the check list 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	

Topic	Practical experience*
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 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
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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 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 "organisational structure of the MAH's local office"

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

A description of the organisational 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 organisations and operational units relevant to the fulfilment of pharmacovigilance obligations. This should include third parties. Specifically, the national PSSF shall describe:

- The organisational structure of the MAH's local office, showing the position of the QPPV in the organisation.
- The site(s) where the pharmacovigilance functions on the national level are undertaken covering individual case safety report collection, evaluation, safety database case entry, periodic safety update report production (integration with global system), signal detection and analysis(integration with global system), risk management plan management, pre- and post-authorisation 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 delegated activities and/or services relating to the fulfilment of pharmacovigilance obligations.

Links with other organisations, 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 organised according to; service providers (e.g. medical information, auditors, patient support programme 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 later 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"

Remember 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 authorised 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 programmes sponsored by the marketing authorisation holder 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 authorised 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/programme, the product(s) and the main objective. It should distinguish between interventional and non-interventional studies and should be organised per active substance. The list should be comprehensive for all studies/programmes and should include ongoing studies/programmes as well as studies/programmes 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 "computerised systems and databases"

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

It is understood that for multinational MAH this global safety database might be located outside the KSA (at the site where the main pharmacovigilance activities are performed globally e.g. Headquarter). However, QPPV must have online access to national safety cases and all national pharmacovigilance data of the KSA; otherwise at least backup database of this national data should always be kept in the local office.

The location, functionality and operational responsibility for computerised 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 computerised systems/databases are used on national level, the applicability of these to pharmacovigilance activities should be described in such a way that a clear overview of the extent of computerisation 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, should be described.

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

Remember 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 risk-benefit 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 minimisation 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 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 marketing authorisation holder 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 minimisation and prevention and appropriate measures are taken by the marketing authorisation holder;
2. the scientific evaluation by the marketing authorisation holder of all information on the risks of medicinal products;
3. the submission of accurate and verifiable data on serious and non-serious adverse reactions to the national medicines 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 marketing authorisation holder with the national medicines authorities, including communication on new risks or changed risks, the pharmacovigilance system master file & national PSSF , risk management systems, risk minimisation measures, periodic safety update reports, corrective and preventive actions, and post-authorisation studies;
6. the update of product information by the marketing authorisation holder in the light of scientific knowledge, and on the basis of a continuous monitoring by the marketing authorisation holder of information released by the national medicines authorities;
7. appropriate communication by the marketing authorisation holder of relevant safety information to healthcare professionals and patients.

These interfaces with other functions include, but are not limited to, the roles and responsibilities of the QPPV, responding to 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"

Remember 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 correct 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, PSURs or other submissions;

An overview of the timeliness of PSUR reporting to the SFDA (the annex should reflect the latest figures used by the marketing authorisation holder 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 authorisation(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"

Remember 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 organisation 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 organisation, 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 organisational chart giving the number of people (full time equivalents) involved in pharmacovigilance activities, which may be provided in the section describing the organisational 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 organisation of specific pharmacovigilance activities. However, a description should be provided in order to explain the training organisation 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

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

For marketing authorisations 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 utilise 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, organised 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 marketing authorisation holder;

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 marketing authorisation holder, 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, marketing authorisation holders 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 Organisational 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

Computerised 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 computerised systems and databases is used, Annex D should simply be described as ‘unused’ in the indexing, in order that recipients of the pharmacovigilance system master file 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 authorisation application; only a summary of the applicant’s national pharmacovigilance sub-system is required to be included in the marketing authorisation application, which shall include the following elements in module 1.8. 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 authorisation applications (i.e. pre-authorisation), 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 authorisation applications (i.e. pre-authorisation) in the following situations:

- the applicant has not previously held a marketing authorisation in the KSA, full PSMF and the national PSSF are appropriate to review the description of a pharmacovigilance system;
- the applicant has not previously submit 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 organisation, 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 marketing authorisation holder has a history of serious and/or persistent pharmacovigilance non-compliance, a pre-authorisation pharmacovigilance inspection may be one mechanism to confirm that improvements have been made to the system before a new authorisation 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 authorisation applications (i.e. pre-authorisation), instead the "summary of PSMF" and "summary of national PSSF" should be submitted. The following table summarises 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 marketing authorisation holder shall keep the pharmacovigilance system master file up to date and, where necessary, revise it to take account of experience gained, of technical and scientific progress and of amendments to Directive 2001/83/EC and Regulation (EC) No 726/2004.
2. The pharmacovigilance system master file and its Annex shall be subject to version control and shall indicate the date when it was last updated by the marketing authorisation holder.
3. Any deviations from the pharmacovigilance procedures, their impact and their management shall be documented in the pharmacovigilance system master file until resolved.
4. Without prejudice to the requirements set out in Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (1), the marketing authorisation holder shall notify immediately the SFDA of any change in the location of the pharmacovigilance system master file or changes to the contact details and name of the qualified person responsible for pharmacovigilance.

Content of the Annex to the pharmacovigilance system master file

The pharmacovigilance system master file shall have an Annex containing the following documents:

- (1) a list of medicinal products covered by the pharmacovigilance system master file, 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 authorisation is valid;

- (2) a list of written policies and procedures for the purpose of complying with Article 11(1);
- (3) the list of subcontracts referred to in Article 6(2);
- (4) a list of the tasks that have been delegated by the qualified person for pharmacovigilance;
- (5) a list of all scheduled and completed audits;
- (6) where applicable, a list of the performance indicators referred to in Article 9;
- (7) where applicable, a list of other pharmacovigilance system master files held by the same marketing authorisation holder;
- (8) a logbook containing the information referred to in Article 5(4).

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 marketing authorisation holders comply with pharmacovigilance obligations established in the KSA, and to facilitate compliance, the SFDA concerned shall conduct, pharmacovigilance inspections of marketing authorisation holders or any firms employed to fulfil marketing authorisation holder's pharmacovigilance obligations. Such inspections shall be carried out by inspectors appointed by the SFDA and empowered to inspect the premises, records, documents and pharmacovigilance system master file (PSMF) of the marketing authorisation holder or any firms employed by the marketing authorisation holder to perform the activities. In particular, marketing authorisation holders are required to provide, on request, the pharmacovigilance system master file, which will be used to inform inspection conduct (see Module II).

The objectives of pharmacovigilance inspections are:

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

For marketing authorisation holders of products, it is the responsibility of the SFDA to ensure that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements. The pharmacovigilance system master file shall be

located either where the main pharmacovigilance activities of the marketing authorisation holder are performed or where the qualified person responsible for pharmacovigilance operates. The supervisory authority may conduct pre-authorisation inspections to verify the accuracy and successful implementation of the existing or proposed pharmacovigilance system.

Pharmacovigilance inspection programmes 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 marketing authorisation holder in a timely manner through the implementation of a corrective and preventive action plan.

If the outcome of the inspection is that the marketing authorisation holder does not comply with the pharmacovigilance obligations,

the SFDA shall take the necessary measures to ensure that a marketing authorisation holder 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 programmes. 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 recognised, and an inspection is considered an appropriate way to examine the issues. For cause inspections are more likely to focus on specific pharmacovigilance processes or to include an examination of identified compliance issues and their impact for a specific product. However, full system inspections may also be performed resulting from a trigger. For cause inspections may arise when, for example, one or more of the triggers listed below are identified but no limited to:

- risk-benefit balance of the product:
 - change in the risk-benefit balance where further examination through an inspection is considered appropriate;
 - delays or failure to identify or communicate a risk or a change in the risk-benefit balance;
 - communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to 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 risk management plan (RMP) commitments;
 - delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorisation;
 - poor quality of reports requested as specific obligations;
- Inspections
 - delays in the implementation or inappropriate implementation of corrective and preventive actions;
 - information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP) ;
 - inspection information received from other international authorities, which may highlight issues of non-compliance;
- others:
 - concerns following review of the pharmacovigilance system master file;
 - non-inspection related information received from other authorities, which may highlight issues of non-compliance;
 - other sources of information or complaints.

III.B.1.3. Pre-authorisation inspections

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

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

If the outcome of the pre-authorisation 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 authorisation;
- a re-inspection prior to approval of the marketing authorisation to confirm that critical findings and recommendations have been addressed;
- granting of the marketing authorisation with the recommendation to perform an early post-authorisation pharmacovigilance inspection. In this case, the findings would influence the timing of an inspection conducted as part of the SFDA routine programme of pharmacovigilance inspections (see III.B.2.);
- imposition of safety conditions to the marketing authorization.

III.B.1.4. Post-authorisation inspections

Post-authorisation pharmacovigilance inspections are inspections performed after a marketing authorisation is granted and are intended to examine whether the marketing authorisation holder complies with its pharmacovigilance obligations. They can be any of the types mentioned under III.B.1.1 and III.B.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 programme. Risk factors will be assessed in order to prioritise 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 marketing authorisation holder or firms employed by the marketing authorisation holder. Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside 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 pharmacovigilance system master file, 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 marketing authorisation holder.

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

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

Factors which may be taken into consideration, as appropriate, by the SFDA when establishing pharmacovigilance inspection programmes 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-minimisation activities;
 - authorisation with conditions associated with safety, e.g. requirement for post-authorisation 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;
- Marketing authorisation holder related:
 - marketing authorisation holder that has never been subject to a pharmacovigilance inspection;
 - marketing authorisation holder with many products on the market in the KSA;
 - resources available to the marketing authorisation holder for the pharmacovigilance activities they undertake;
 - marketing authorisation holder with no previous marketing authorisations 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 marketing authorisation holder organisation, such as mergers and acquisitions;
- pharmacovigilance system related:
 - marketing authorisation holder with sub-contracted pharmacovigilance activities (function of the qualified person responsible for pharmacovigilance in the KSA (QPPV), reporting of safety data etc.) 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 pharmacovigilance system master file management.

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

III.B.3. Sites to be inspected

Any party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorisation holder may be inspected, in order to confirm their capability to support the marketing authorisation holder'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 centre, 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 third 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 pharmacovigilance system master file;
- information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from the SFDA such as the National Pharmacovigilance and Drug Safety Center (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:

- individual case safety reports (ICSRs):
 - collecting, receiving and exchanging reports - from all types of sources, sites and departments within the pharmacovigilance system, including from those firms employed to fulfil marketing authorisation holder's pharmacovigilance obligations and departments other than drug safety;
 - assessment, including mechanisms for obtaining and recording reporter assessments, company application of event terms, seriousness, expectedness and causality. In addition to examples of 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;
- periodic safety update reports (PSURs), (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 authorisation;
- 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)
- 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 PSURs), where applicable, PASS or post-authorisation 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 pharmacovigilance system master file, performance metrics, audit and inspection reports, and their ability to take action to improve compliance;
- the roles and responsibilities of the marketing authorisation holder in relation to the pharmacovigilance system;
- accuracy, completeness and maintenance of the pharmacovigilance system master file;
- quality and adequacy of training, qualifications and experience of staff;
- coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes;
- fitness for purpose of computerised systems;
- contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfilment of pharmacovigilance, and are adhered to.
- As a general approach, a marketing authorisation holder should be inspected on the basis of risk-based considerations, but at least once every 4 years.

The inspection may include the system for the fulfilment of conditions of a marketing authorisation and the implementation of risk–minimisation 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 marketing authorisation holder, or not covered in a prior inspection.

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

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

- sharing of information;
- inspection planning;
- pre-authorisation inspections;
- coordination of pharmacovigilance inspections in the KSA;
- coordination of third country inspections (including inspections of contractors in third countries);
- preparation of pharmacovigilance inspections;

- conduct of pharmacovigilance inspections;
- reporting of pharmacovigilance inspections and inspection follow-up;
- communication and prioritisation of pharmacovigilance inspections and findings;
- interaction with 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 marketing authorisation holder's corrective and preventive action plan;
- review of the periodic progress reports, when deemed necessary;
- re-inspection to assess appropriate implementation of the corrective and preventive action plan;
- requests for submission of previously un-submitted data; submission of variations, e.g. to amend product information; submission of impact analyses, e.g. following review of data that were not previously considered during routine signal detection activities;

- requests for issuing safety communications, including amendments of marketing and/or advertising information;
- requests for a meeting with the marketing authorisation holder 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 authorisations or clinical trial authorisations).

Sharing information and communication between inspectors and assessors is important for the proper follow-up of inspections. Details of the processes relating to interaction between inspectors and assessors and inspection follow-up will be elaborated further.

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 public health impact of the non-compliance(s), but any instance of non-compliance may be considered for enforcement action. The SFDA shall take the necessary measures to ensure that a marketing authorisation holder 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 marketing authorisation holder representatives (e.g. in a meeting) to summarise the identified non-compliances, to clarify the legal requirements and the expectations of the

regulator, and to review the marketing authorisation holder's proposals for corrective and preventive actions;

- inspection: non-compliant marketing authorisation holders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- warning letter, non-compliance statement or infringement notice.
- authorisation holders of their pharmacovigilance obligations or specifying the steps that the marketing authorisation holder must take and in what timeframe in order to rectify the non-compliance and in order to prevent a further case of non-compliance;
- The SFDA may consider making public a list of marketing authorisation holders found to be seriously or persistently non-compliant;
- actions against a marketing authorisation(s) or authorisation application(s) e.g.
 - Urgent Safety Restriction;
 - variation of the marketing authorisation;
 - suspension or revocation of the marketing authorisation;
 - delays in approvals of new marketing authorisation applications until corrective and preventive actions have been implemented or the addition of safety conditions to new authorisations;
 - requests for pre-authorisation 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 will be described in the procedure on Record Keeping and Archiving of Documents Obtained or Resulting from the Pharmacovigilance Inspections referred to in III.B.5.

III.B.9. Qualification and training of inspectors

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by the SFDA or 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. In addition, consideration should be given to the recommendations for training and experience described in III.B.5.

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 programme for routine inspections for authorised products will be determined by the SFDA. These inspections will be prioritised based on the potential risk to public health, considering the factors listed in III.B.5. If the same pharmacovigilance system is used for a variety of authorisation types, then the results of a supervisory authority inspection may be applicable for all products covered by that system.

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

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 marketing authorisation holder’s pharmacovigilance system.

Based on the information from other inspections, the SFDA will prioritise the inspections in its programme 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-minimisation measures, communications concerning safety, locally conducted safety studies, or issues linked to

health care 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 Marketing Authorisation Holders and Applicants

Marketing authorisation holders with authorised 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 pharmacovigilance system master file.
- To ensure that the sites selected for inspection, which may include firms employed by the marketing authorisation holder 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 prioritisation 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.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

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 harmonisation, 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 standardisation organisations*¹ 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 marketing authorisation holders or the SFDA, to plan, conduct and report upon an individual pharmacovigilance audit engagements. This Section also provides an outline of the general quality system and record management practices for pharmacovigilance audit processes.

¹ More details regarding **The Institute of Internal Auditors (IIA)** www.theiia.org; the **International Organisation for Standardisation (ISO)** www.iso.org; **Information Systems Audit and Control Association (ISACA)** www.isaca.org; **The International Auditing and Assurance Standards Board (IAASB)** www.ifac.org; **The International Organisation of Supreme Audit Institutions (INTOSAI)** www.issai.org.

IV.A.1. Terminology

Audit, Audit findings, Audit plan, Audit programme, Audit recommendations,

Auditee: [entity] being audited (ISO 19011 (3.7))².

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, organises, 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 organisation'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 organisational 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

² The Institute of Internal Auditors (IIA) www.theiia.org

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).

International Auditing Standardisation Organisations: More details regarding **The Institute of Internal Auditors** (IIA) standards can be found at <http://www.theiia.org/guidance/standards-and-guidance/ippf/standards/full-standards> ; the **International Organisation for Standardisation** (ISO) standard 19011 “Guidelines for quality and/or environmental management systems auditing. <http://www.iso.org/iso/home.html> ; **Information Systems Audit and Control Association** (ISACA) standards can be found at <http://www.isaca.org/Standards> ; **The International Auditing and Assurance Standards Board** (IAASB) standards can be found at <http://www.ifac.org/auditing-assurance/clarity-center/clarified-standards> ; The International Organisation of Supreme Audit Institutions (INTOSAI) can be found at <http://www.issai.org/composite-347.htm>.

the Committee of Sponsoring Organizations (COSO) standards

<http://www.coso.org/>

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 organisation'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 programme, setting audit objectives, and the extent and boundaries, often termed as scope, of the audits in that programme; and
- operational level audit planning resulting in an audit plan for individual audit engagements, prioritising audit tasks based on risk and utilising risk-based sampling and testing approaches, and reporting of audit findings in line with their relative risk level and audit recommendations in line with the suggested grading system [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 organisation (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 programme, usually for a period of 2-5 years. The audit strategy includes a list of audits that could reasonably be performed. The audit strategy is used to outline the areas highlighted for audit, the audit topics as well as the methods and assumptions (including e.g. risk assessment) on which the audit programme is based.

The audit strategy 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 organisations or activities delegated to another organisation (e.g. regional reporting centres, MAH affiliates or third parties, such as contract organisations and other vendors).

This is a non-prioritised, 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-organisation or other re-structuring of the pharmacovigilance system, mergers, acquisitions (specifically for marketing authorisation holders, this may lead to a significant increase in the number of products for which the system is used);
- change in key managerial function(s);
- risk to availability of adequately trained and experienced pharmacovigilance staff, e.g. due to significant turn-over of staff, deficiencies in training processes, re-organisation, 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 marketing authorisation holder);

medicinal product(s) on the market with specific risk minimisation measures or other specific safety conditions such as requirements for additional monitoring;

- criticality of the process, e.g.:

o for the SFDA: how critical is the area/process to proper functioning of the pharmacovigilance system and the overall objective of safeguarding public health;

o for marketing authorisation holders: how critical is the area/process to proper functioning of the pharmacovigilance system. When deciding when to audit an affiliate or third party, the marketing authorisation holder should consider the nature and criticality of the pharmacovigilance activities that are being performed by an affiliate or third party on behalf of the marketing authorisation holder, in addition to considering the other factors included in this list;

- outcome of previous audits, e.g. has the area/process ever been audited (if not, then this may need to be prioritised 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;

IV.B.2.2. Tactical level audit planning

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

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

The audit programme documentation 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 programme 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 programme 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 organisation 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 organisation 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 programme (see IV.B.2.2.). grading, 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 auditees 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 prioritised. 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 organisation is responsible for ensuring that the organisation 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 programme. 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 organisation should assign the specific responsibilities for the pharmacovigilance audit activities. Pharmacovigilance audit activities should be independent. The organisation'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);
- organisational 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 programme, 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 organisation (i.e. marketing authorisation holder). Where the organisation 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 programme and individual engagements should be specified to the outsourced service providers, by the organisation, in writing;
- the scope, objectives and procedural requirements for the audit should be specified to the outsourced service provider, by the organisation, in writing;
- the organisation 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 section I.B.10.IV.C.

IV.C. Pharmacovigilance audit policy framework and organisational structure

IV.C.1. Marketing authorisation holders in the KSA

IV.C.1.1. Requirement to perform an audit

The marketing authorisation holder 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 marketing authorisation holder.

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 marketing authorisation holder

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

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

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 recognised that at the time of authorisation, 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-morbidity, restricted co-medication, 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 authorised on the basis that in the specified indication(s), at the time of authorisation, 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 authorisation is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post-authorisation. Planning of the necessary pharmacovigilance activities to characterise the safety profile of the medicinal product will be improved if it is more closely based on specific issues identified from pre- or post-authorisation data and from pharmacological principles.

However, the purpose of risk identification and characterisation is to allow for risk minimisation or mitigation wherever possible. Therefore risk management has three stages which are inter-related and re-iterative:

1. Characterisation of the safety profile of the medicinal product including what is known and not known.

2. Planning of pharmacovigilance activities to characterise risks and identify new risks and increase the knowledge in general about the safety profile of the medicinal product.
3. Planning and implementation of risk minimisation and mitigation and assessment of the effectiveness of these activities.

The chapter on risk management systems for medicinal products for human use in Volume 9A, which this guidance replaces, was based solely on managing risks. However, when considering how to maximise, or indeed assess, the risk-benefit balance, risks need to be understood in the context of benefit. In assessing the risk-benefit balance at the time of authorisation, the assumption is made that these benefits and risks apply to the whole target population. However, there may be subsets of patients for whom the risk is greater than that for the target population as a whole, or in whom the benefit may not be as great. In addition, efficacy in the clinical trial setting may not reflect the true effectiveness of the medicinal product in everyday medical practice and so the risk-benefit balance of a medicinal product as assessed at the time of authorisation will inevitably change post-authorisation.

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

Risk management, is applicable to medicinal products at any point in their lifecycle. However, this module concentrates on peri- and post-authorisation risk management and is applicable to all products authorized.

The risks addressed in this guidance are those related to non-clinical and clinical safety. In addition, quality issues may be relevant if they impact on the safety and/or efficacy of the product. Where the disposal of the product might pose a particular risk because of remaining active substance (e.g. patches) this should also be addressed.

Although this module includes the principles of risk minimisation, and details of routine risk minimisation measures, more detail on, in particular, additional risk minimisation tools and the measurement of the effectiveness of risk management can be found in Module XVI.

V.B. Structures and processes

V.B.1. Terminology

Identified risk

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

- an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;

- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

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

Potential risk

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

Examples include:

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

Missing information

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations,

which could be clinically significant.

Examples of missing information include populations not studied (e.g. pregnant women or patients

with severe renal impairment) or where there is a high likelihood of off-label use.

Important identified risk and important potential risk

An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.

What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.

Risk management system

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

Risk management plan

A detailed description of the risk management system

Risk minimisation activity (used synonymously with risk minimisation measure)

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

Safety concern

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

Target population (treatment)

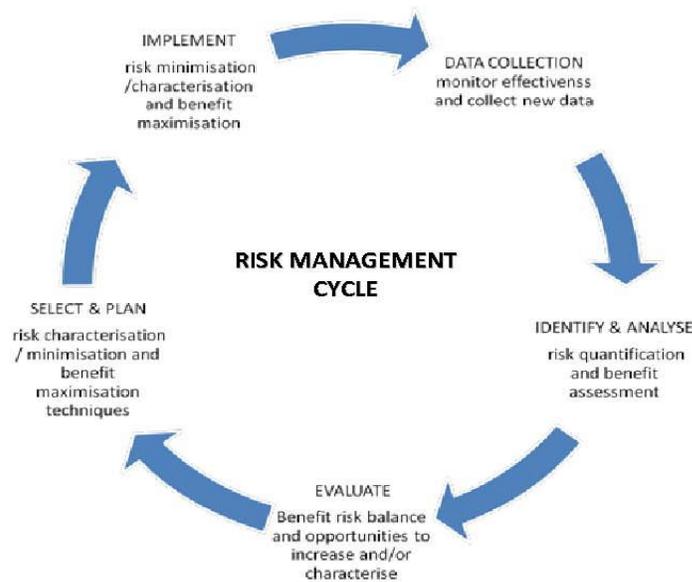
The patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information.

V.B.2. Principles of risk management

The overall aim of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This can be done either by increasing the benefits or by reducing the risks. Although the primary aim and focus of the RMP remains that of risk management, the evaluation of the need for efficacy studies (including those linked to the Safety Specification section on Missing Information) and their integration, where necessary, in the RMP may enable resources to be used more efficiently and for risks to be put into context. The RMP therefore includes the planning of such studies and is without prejudice to the specific efficacy guidance and measures foreseen in local regulations.

The principles of risk management are the same regardless of stakeholder (see below).

Figure V.1. The risk management cycle



However, the actions and responsibilities within each step of the cycle will vary according to whether the stakeholder is an applicant/marketing authorisation holder. Other players may be involved in risk-benefit management such as: patient organisations, learned societies, health economists, national safety organisations, environmental advisors, occupational health professionals and pharmaceutical distributors but their roles will usually be smaller and complementary to that of the main players.

In the KSA, as well as complying with the legislation, the primary document and process for risk management adheres to the principles in the International Conference for Harmonisation (ICH) Guideline E2E on Pharmacovigilance Planning. For healthcare professionals, product information, medical treatment guidelines and any materials

produced by marketing authorisation holders will direct prescribing, dispensing, treatment and management of both benefit and risks. For patients, the majority of medicinal products will be prescribed by doctors and dispensed by pharmacists so that management of benefits and risks will primarily involve complying with treatment schedules and recommendations, being aware of important risks and what actions to take, and reporting to their doctor, pharmacist and other HCPs any untoward effects. However, in some situations, patients may buy medicines directly without guidance from healthcare practitioners so will need to understand the potential benefits and risks of the product and what measures they need to comply with to use the medicine safely and effectively. Whatever the setting, patients who understand the potential benefits and risks of a medicinal product are better equipped to decide whether or not to be treated and to comply with suggested risk minimisation activities.

V.B.3. Responsibilities for risk management within an organisation

The principle organisations directly involved in medicinal products' risk management planning are applicants/marketing authorisation holders and the SFDA.

V.B.3.1. Marketing authorisation holders and applicants

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

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

Other Modules within GVP deal with specific aspects of the above so this Module is confined to the risk management plan and its contents.

ICH-E2E defines two basic parts of a RMP: the safety specification and the pharmacovigilance plan. It does not include risk minimisation. However it was acknowledged at the time of development of ICH-E2E that risk minimisation was an integral part of risk management planning. Details of how the safety specification and pharmacovigilance plan are integrated within the RMP and the detailed structure and format are provided in V.B.5 to V.B.7.

Producing a RMP requires the input of different specialists and departments within and/or outside an organisation. The safety specification may require involvement of toxicologists, clinical Pharmacists, clinical research physicians, pharmacoepidemiologists and pharmacovigilance experts. The input required for the pharmacovigilance plan may require any of these experts depending upon the safety concerns identified in the safety specification and the types of activities planned to address them. The design of risk minimisation activities should involve people with expertise in communication and, where appropriate, patients and/or healthcare professionals. Since a risk management plan is primarily a pharmacovigilance document, ideally the production of it should be managed by personnel with appropriate pharmacovigilance training in either the pharmacovigilance or regulatory departments, depending upon company structure. Regardless of who prepares the RMP, the responsibility for the content and accuracy of the RMP remains with the marketing authorisation applicant/holder who should ensure oversight by someone with the appropriate scientific background within the company.

Further guidance on individual risk minimisation activities is provided in Module XVI.

V.B.3.2. SFDA

The general responsibilities of the SFDA are discussed in Module I. In relation to risk management, the principal responsibilities of the SFDA are:

- constantly monitoring the benefits and risks of medicinal products including assessing the reports submitted by pharmaceutical companies, healthcare professionals, patients and, where appropriate, other sources of information;
 - taking appropriate regulatory actions to minimise the risks of the medicinal product and maximise the benefits including ensuring the accuracy and completeness of all information produced by the company in relation to its medicinal products;
 - ensuring the implementation of risk minimisation activities;
 - effectively communicating with stakeholders when new information becomes available. This includes providing information in an appropriate format to patients, healthcare physicians, patient groups, learned societies etc;
 - when necessary, ensuring that marketing authorisation holders of generic and/or similar biological medicinal products make similar changes to their risk minimisation measures when changes are made to those of the reference medicinal product;
- providing information to other regulatory authorities, this includes notification of any safety activities in relation to a product, including changes to the product information of originator and/or reference medicinal products.

V.B.4. Objectives of a risk management plan

The RMP must contain the following elements which:

- identify or characterise the safety profile of the medicinal product(s) concerned;
- indicate how to characterise further the safety profile of the medicinal product(s) concerned;

- document measures to prevent or minimise the risks associated with the medicinal product including an assessment of the effectiveness of those interventions;
- document post-authorisation obligations that have been imposed as a condition of the marketing authorisation.

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

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

The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the products. For products requiring periodic safety update reports (PSURs), certain (parts of) modules may be used for both purposes (see V.B.14.).

V.B.5. Structure of the risk management plan

The RMP consists of seven parts. Certain parts of the RMP, in particular the safety specification, are subdivided into modules, so the content can be tailored to the specifics of the medicinal product and modules added/removed or re-used in other documents (e.g. PSURs). RMP part II modules generally follow the section titles in the Safety Specification of ICH-E2E, whilst RMP part III follows the Pharmacovigilance Plan. Differences between

indications, formulations and target populations, if several medicinal products have the same active substance, will be similarly accommodated by dividing the relevant parts of the RMP into modules and/or sections. The modular structure also means that the RMP can be updated easily. As the product matures, some RMP modules or sections may cease changing – for example non clinical studies may stop at a certain time as may clinical trials. These RMP modules can be effectively “locked” until new data needs to be added. In addition, certain RMP modules may be omitted in specific circumstances (see V.C.2.1.).

The submitted RMP should follow the RMP template- annexed with this document. The amount of information, particularly in RMP part II, which can be provided will depend on the type of medicinal product and where it is in its lifecycle but this guidance provides an overview of the level of information needed and its format.

The risk management system shall be proportionate to the identified risks and the potential risks of the medicinal product, and the need for post-authorisation safety data. This proportionality can be achieved in different ways: by reducing the number of modules which need to be submitted for products meeting certain conditions (such as well established products/generics see table V.3), and by ensuring that requirements for post-authorisation studies and risk minimisation activities reflect the important risks and important uncertainties of the product.

An overview of the parts and modules of the RMP is provided below [IR Annex I]:

Figure V.2. Overview of the parts and modules of the RMP

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-authorisation 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

Part IV Plans for post-authorisation efficacy studies

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

Part VI Summary of the risk management plan

Part VII Annexes

Where a RMP concerns more than one medicinal product, a separate RMP part VI must be provided for each medicinal product.

Information should be provided in enough detail to enable an assessor to understand the issues being presented. Unless specifically mentioned in this guidance, cross references to other parts of the dossier should be avoided since it is intended that the RMP should be a largely stand-alone document that is a scientific synopsis of the relevant parts of the dossier, emphasising the important clinically relevant facts. To aid consistency between the information provided in the CTD and the RMP, the table below indicates the location of information in the CTD is summarised for the RMP:

RMP	CTD
Part I Active substance information	Module 2.3 Quality overall summary Module 3 Quality

RMP	CTD
Module SI Epidemiology of the target population	Module 2.5 Clinical overview
Module SII Non-clinical part of 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 - briefly Module 5 Clinical Study reports
Module SIV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post authorisation experience	Module 2.5 Clinical overview - briefly
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 activities	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part IV Plans for post authorisation efficacy studies (including presentation of efficacy data)	Module 2.5 Clinical overview Module 2.7 Clinical summary

RMP	CTD
Part V Risk minimisation measures	Module 2.5 Clinical overview Module 2.7 Clinical summary

Copies of literature referenced in the RMP should be included in RMP annex 12.

V.B.6. Detailed description of each part of the risk management plan

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

Certain products for human medicinal use are categorised within the SFDA as advanced therapy medicinal products (ATMPs), Including the following:

Certain products for human medicinal use are categorised as advanced therapy medicinal products (ATMPs). These products are broadly comprise:

- gene therapy medicinal products;
- somatic cell therapy medicinal products;
- tissue engineered products.

Because of the nature of these products, risks may occur which are not normally a consideration with other medicinal products including risks to living donors, risks of germ line transformation and transmission of vectors. For this reason, for ATMPs, RMP module

VII Identified and potential risks (ATMP) should replace RMP module VII Identified and potential risks as this provides greater flexibility in consideration of the additional risks.

V.B.7. RMP part I “Product overview”

This should provide the administrative information on the RMP and an overview of the product(s) covered within it.

The information should include:

Active substance information:

- active substance(s);
- pharmacotherapeutic group(s) (ATC code);
- name of marketing authorisation holder or applicant;
- date and country of first authorisation worldwide (if applicable);
- date and country of first launch worldwide (if applicable);
- number of medicinal product(s) to which this RMP refers.

Administrative information on the RMP:

- data lock point of the current RMP;
- date submitted and the version number;
- list of all parts and modules of the RMP with date and version of the RMP when the part/module was last (updated and) submitted.
- invented name(s) in KSA;
- brief description of the product including:
 - chemical class;

- summary of mode of action;
- important information about its composition (e.g. origin of active substance of biologicals, relevant adjuvants or residues for vaccines);
- indications:
 - current (if applicable) in KSA;
 - proposed (if applicable) in KSA;
- dosage in KSA:
 - proposed in the EEA (for multinational MAH/MAA with the product authorised in EU)
 - or current of the reference medicinal product in the EEA (for generics);dosage:
 - current (if applicable) in KSA;
 - proposed (if applicable) in KSA;
- pharmaceutical forms and strengths:
 - current (if applicable) in KSA;
 - proposed (if applicable) in KSA;
- whether the product is the subject of additional monitoring in KSA.

V.B.8. RMP part II “Safety specification”

The purpose of the safety specification is to provide a synopsis of the safety profile of the medicinal product(s) and should include what is known and not known about the medicinal product(s). It should be 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 labelled and off-labelled use), and outstanding safety questions which warrant further investigation to refine

understanding of the risk-benefit profile during the post-authorisation period. In the RMP, the safety specification will form the basis of the pharmacovigilance plan, and the risk minimisation 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 in the KSA.

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-authorisation experience

Module SVI Additional requirements for the safety specification

Module SVII Identified and potential risks

Module SVIII Summary of the safety concerns

RMP modules SIII–SV form the “Limitations of the human safety database” part of the ICH-E2E safety specification and these, with the addition of RMP modules SI and SVII form the clinical part of the safety specification.

The applicants/marketing authorisation holders should follow the structure of elements provided below when compiling the safety specification. The elements of the safety specification that are included are only a guide. The safety specification can include additional elements, depending on the nature of the product and its development programme. Elements which might need to be incorporated include:

- quality aspects if relevant in relation to the safety and efficacy of the product,
- the disposal of the product where it might pose a particular risk because of remaining active substance (e.g. patches),
- innovative pharmaceutical forms or
- use with a medical device.

V.B.8.1. RMP module SI “Epidemiology of the indications and target population”

The epidemiology of the indication(s) should be discussed. This discussion should include incidence, prevalence, mortality and relevant co-morbidity, and should whenever possible be stratified by age, sex, and racial and/or ethnic origin. Differences in the epidemiology in the different regions should be discussed, where feasible.

Information should be provided on the important co-morbidities in the target population. For example: if a medicinal product is intended for treating prostate cancer, the target population is likely to be men over the age of 50 years. Men over the age of 50 are also at risk of myocardial infarction. To identify whether a medicinal product might be increasing the risk of myocardial infarction, it is important to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not taking the medicinal product. Estimation of the risk in the target population, as compared with the same age/sex group in the general population may be particularly important if the disease itself increases the risk of a particular adverse event.

The RMP should include a statement of the intended purpose and impact of the product e.g. whether it is intended to prevent disease, to prevent particular serious outcomes due to a condition or to reduce progression of a chronic disease.

V.B.8.2. RMP module SII “Non-clinical part of the safety specification”

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

- toxicity (key issues identified from e.g. repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
- general pharmacology (e.g. cardiovascular, including QT interval prolongation, nervous system);

- drug interactions;
- other toxicity-related information or data.

What constitutes an important 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. important information on the active substance or its impurities, 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 risk to the target population, it should be included as a safety concern in RMP module SVIII.

For other special populations depending upon the indication and target population, consideration should be given to whether specific non-clinical data needs exist.

V.B.8.3. RMP module SIII “Clinical trial exposure”

In order to assess the limitations of the human safety database, data on the patients studied in clinical trials should be provided. This data should be provided in the most appropriate format, e.g. tables/graphs. The size of the study population should be detailed using both numbers of patients and, where appropriate, patient time (patient-years, patient-months) exposed to the medicinal product. This should be stratified for relevant categories and also by the type of trial (randomised blinded trial population only and all clinical trial populations.) Stratifications would normally include:

- age and gender;

- indication;
- dose;
- racial origin (see also V.B.8.4).

Duration of exposure should be provided either graphically by plotting numbers of patients against time or in tabular format.

The exposure of special populations (pregnant women, breast-feeding women, renal impairment, hepatic impairment, cardiac impairment, sub-populations with relevant genetic polymorphisms, immuno-compromised) should be provided as appropriate. The degree of renal, hepatic or cardiac impairment should be specified as well as the genetic polymorphism.

The categories above are only suggestions and tables/graphs should be tailored to the product. For example, indication may not be a relevant stratification for a medicinal product where only one indication has been studied, and route of administration, number of courses/immunisations or repeat administrations may be important categories to be added.

When presenting age data, categories should be chosen which are relevant to the target population. Broad artificial divisions which are not clinically relevant, such as <65 and >65, should be avoided. Paediatric data should be divided by categories (e.g. ICH-E11); similarly the data on elderly patients should be considered for stratification into categories such as 65-74, 75-84 and 85+, although the age strata should reflect that of the target population. For teratogenic drugs, stratification into age categories relating to childbearing potential might be appropriate for the female population.

Unless clearly relevant, data should not be presented by individual trial but should be 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/sex/ethnic origin tables. Where differences in the

total numbers of patients arise between tables, the tables should be annotated to reflect the reasons for discrepancy.

When the RMP is being submitted with an application for a new indication, a new pharmaceutical form or route, the clinical trial data specific to the application should be presented separately at the start of the module as well as being included in the summary tables (as described above) representing pooled data across all indications.

V.B.8.4. RMP module SIV “Populations not studied in clinical trials”

RMP module SIV should discuss which sub-populations within the expected target population have not been studied or have only been studied to a limited degree in the clinical trial population. Limitations of the clinical trials should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population. This is particularly important when exclusion criteria are not proposed as contraindications for the drug. Lists of inclusion/exclusion criteria should not be provided by trial, but a summary of the effect of these in the overall development programme in relation to the target population should be provided. 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.

The implications, with respect to predicting the safety of the product in the marketplace, of any of these populations with limited or no research should be explicitly discussed. In addition, the limitations of the database with regard to the detection of adverse reactions due to:

1. number of patients studied;
2. cumulative exposure (e.g. specific organ toxicity);
3. long term use (e.g. malignancy);

should be discussed. Where the missing information could constitute an important risk to the target population, it should be included as a safety concern in RMP module SVIII.

Populations to be considered for discussion should include (but might not be limited to):

- Paediatric population

Children (from birth to 18 years with consideration given to the different age categories as per ICH-E11, or, if justified, to other developmentally meaningful groups i.e. taking into account specific organ maturation). If paediatric development has been limited to certain age categories then the implications for other paediatric age groups should also be discussed.

- Elderly population

Implications for use in patients over the age of 65 should be discussed – with appropriate consideration given to use in the older end of the age spectrum. The effects of particular impairments, e.g. renal, hepatic, or of concomitant disease or medication will be discussed mainly in the appropriate sections below, but discussion in this section should reflect the fact that in the elderly population many of these factors may co-exist. The cumulative effect of multiple impairments and multiple medications should be discussed. Consideration of whether particular laboratory screening should be performed routinely before use of the medicinal product(s) in the elderly should be discussed. In particular any adverse reactions which might be of special concern in the elderly e.g. dizziness or central nervous system effects should be explored.

- Pregnant or breast-feeding women

If the target population includes women of child-bearing age, the implications for pregnancy and/or breast-feeding should be discussed. If the medicinal product is not specifically for use during pregnancy, any pregnancies which have occurred during the developmental programme and their outcomes should be discussed. For products where pregnancy should be avoided for safety reasons, the discussion on pregnancy should also include an analysis of the reasons why the contraceptive measures in place during the clinical trials failed and the implications for use in the less controlled conditions of everyday medical practice.

- Patients with hepatic impairment
- Patients with renal impairment
- Patients with other relevant co-morbidity (e.g. cardiovascular or immunocompromised including organ transplant patients)
- Patients with disease severity different from that studied in clinical trials

Any experience of use in patients with different disease severities should be discussed, particularly if the proposed indication is restricted to those patients with a specific disease severity.

- Sub-populations carrying known and relevant genetic polymorphism

The extent of pharmacogenetic effects and the implications on genetic biomarker use in the target population should be discussed. Where a proposed drug indication constitutes patients with or without specific genetic markers, or the clinical development programme

has been in patients with a specific mutation, the marketing authorisation holder should discuss the implications of this for the target population and explore whether use in patients with an unknown or different genotype could constitute a safety concern.

If a potentially clinically important genetic polymorphism has been identified but not fully studied in the clinical development programme, this should be considered as missing information and/or a potential risk. This should be reflected in the safety specification and pharmacovigilance plan. Whether it is included as a safety concern for the purposes of risk minimisation will depend upon the importance of the possible clinical implications.

- Patients of different racial and/or ethnic origins

Genetic variants can influence pharmacodynamics and pharmacokinetics, and subsequently affect the efficacy and/or safety of the administered drug. Inter-ethnic differences in drug efficacy and safety have been observed in different ethnic groups due to e.g. genetic polymorphisms.

One example of such inter-ethnic differences is the variation in frequency of the HLA-B*1502 allele. This allele is strongly associated with the occurrence of severe cutaneous adverse reactions to carbamazepine and has a prevalence of about 10% in some Asian populations, whilst the prevalence of the allele is negligible in those of European descent. This is why genomic testing is recommended for patients of some Asian origins when carbamazepine use is planned, while this testing will not make sense for a patient who is of European descent.

Major inter-ethnic differences in pharmacokinetics of drugs may also occur due to types and/or frequencies of gene variants coding for drug metabolising enzymes. The consequences of these inter-ethnic differences could be that the proportion of subjects with particular beneficial effects or adverse reactions varies, leading to different benefit risk profiles and specific recommendations in these ethnic populations.

Furthermore, efficacy in patients may be affected by racial origin. One example is that ACE inhibitors are less potent in black patients of African or Caribbean family origin than in white patients.

Therefore, information on racial origin may be relevant and valuable for evaluation of efficacy and safety and for preventing adverse reactions or improving benefits in the target population.

The experience of drug use in patients with different racial and/or ethnic origins should be discussed including the implications on efficacy and safety, based on pharmacokinetics and pharmacodynamics, in the target population. If it is likely that efficacy or safety may be affected by race or ethnicity, consideration should be given to including this either as a safety concern or as a topic for inclusion in RMP Part IV. Consideration should also be given as to whether post-authorisation efficacy and/or safety studies are necessary.

V.B.8.5. RMP module SV “Post-authorisation experience”

The purpose of this RMP module is to provide information on the number of patients exposed post authorisation; how the medicinal product has been used in practice and labelled and off-label use including use in the special populations mentioned in RMP module SIV. It should also include brief information on the number of patients included in completed observational studies conducted either to elucidate a safety issue or for drug utilisation purposes. Details of significant actions taken to update information on the safety of the medicinal product should also be provided in this module.

V.B.8.5.1. RMP module SV section “Action taken by regulatory authorities and/or marketing authorisation holders for safety reasons”

List any significant regulatory action (including those initiated by the marketing authorisation holder), in any market, taken in relation to a safety concern. Significant

regulatory action would include: a restriction to the approved indication, a new contra-indication, a new or strengthened warning in section 4.4 of the SPC (or equivalent) or any action to suspend or revoke a marketing authorisation. This list should be cumulative, and specify the country, action taken and the date as appropriate. Roll-out in multiple countries of a new safety statement initiated by the MAH can be presented as one action.

When the RMP is updated, a brief description of the reasons leading to any significant actions since the last submission of the RMP should be provided. It may be appropriate to add comments if the regulatory action taken is not applicable to certain products/formulations as authorised in the KSA.

V.B.8.5.2. RMP module SV section “Non-study post-authorisation exposure”

Where marketing of the medicinal product has occurred, the applicant/marketing authorisation holder should provide cumulative data on patients exposed post-marketing. Where possible, the information should be stratified by relevant variables. These may include age, sex, indication, dose and region (Saudi versus other countries worldwide). Depending upon the medicinal product, other variables may be relevant such as number of vaccination courses, route of administration or duration of treatment.

When deciding which measure to use for exposure data, it is important to consider the way a medicinal product is used. Exposure data based on the number of kilogrammes of medicinal product sold divided by the average dose is only valid if the medicinal product is always used at one dose level for a fixed length of time, which is not the situation with most medicinal products. In paediatric populations or mixed populations of different indications or age groups, use of this measure alone is inappropriate and other measures should be used. For example, for medicinal products used chronically, the appropriate measure may be patient years of use. However, when use is typically limited and utilisation

is determined by pack size (e.g. a course of antibiotics), a simple count of packs sold may be more appropriate.

If the drug has different routes of administration, e.g. subcutaneous or oral, exposure data should be presented separately, where possible. SFDA may request additional stratification of exposure data, e.g. exposure in age groups or within different approved indications. However, if the drug is used in different indications with different dosing schedules or other delineating factors suitable for stratification, marketing authorisation holders should consider routinely providing such data where possible.

A more accurate breakdown of drug exposure based on market research should be provided where possible.

If a drug utilisation study has been performed, for reimbursement or other reasons, the results, as they reflect use in the real world setting, should be provided.

V.B.8.5.3. RMP module SV section “Post-authorisation use in populations not studied in clinical trials”

Where there are data on post-authorisation use in the special populations identified in RMP module SIV as having no or limited exposure, estimation of the numbers exposed and the method of calculation should be provided whether or not the usage is on- or off-label. For paediatric use, cross reference may be made to RMP section “Specific paediatric issues” in RMP module SVI (see V.B.8.6.6.). Information on the safety profile of the medicinal product in these special populations, as compared with the rest of the target population, should also be provided. In particular, any information regarding an increased or decreased benefit in a special population should be provided. Any special populations found to be at an increased or decreased risk in relation to a particular safety concern should be discussed under the specific risk in RMP module SVII but reference should be made in this section as to which risks and populations are affected.

V.B.8.5.4. RMP module SV section “Post-authorisation off-label use”

Post marketing, updates to the safety specification, should include information on KSA off-label use; i.e. the intentional use, for a medical purpose, which is not in accordance with the authorised product information for a medicinal product. Off-label use includes use in non-authorised paediatric age categories. Use in clinical trials conducted as part of the marketing authorisation holder’s development programme should be included only in RMP module SIII and not in this section.

Information from drug utilisation studies (or other observational studies where indication is a variable) should be provided where available. This includes drug utilisation studies which were requested by the SFDA for purposes other than risk management. When off label use is a safety concern or a concern has been raised by the SFDA regarding off-label use, marketing authorisation holders should attempt to quantify such use along with a description of the methods used to arrive at these figures

V.B.8.5.5. RMP module SV section “Epidemiological study exposure”

Marketing authorisation holders should provide a listing of epidemiological studies which are, or have been, conducted to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures. This listing should include studies undertaken by the marketing authorisation holder itself or funded by them via a grant, whether specific or unconditional. Studies undertaken by a marketing partner, or where the MAH has been sent the results by a third party, should also be included. Information on the study title, study type (e.g. cohort, case control), population studied (including country and other relevant population descriptors), duration of study, number of persons in each category (e.g. cases, controls, exposure), disease as appropriate, person time (if appropriate) and study status (completed or on-going) should be provided. If a study has

been published, a reference should be included in this RMP section, a synopsis should be included in RMP annex 5 and the publication provided in RMP annex 12.

V.B.8.6. RMP module SVI “Additional requirements for the safety specification”

Some safety topics were not included in ICH-E2E but are thought to be of particular interest due to either legislation or prior experience of a safety issue.

V.B.8.6.1. RMP module SVI section “Potential for harm from overdose”

Special attention should be given to medicinal products where there is an increased risk of harm from overdose, whether intentional or accidental. Examples include medicinal products 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. The potential for harm from overdose should be discussed in this section and, where appropriate, overdose should be included as a safety concern in RMP module SVIII and appropriate risk minimisation proposed in RMP part V.

V.B.8.6.2. RMP module SVI section “Potential for transmission of infectious agents”

The applicant/marketing authorisation holder should discuss the potential for the transmission of an infectious agent. This may be because of the nature of the manufacturing process or the materials involved. For vaccines, any potential for transmission of live virus should be discussed. For advanced therapy medicinal products cross reference to RMP module SVII (ATMP) may be made.

V.B.8.6.3. RMP module SVI section “Potential for misuse for illegal purposes”

The potential for misuse for illegal purposes should be considered. Misuse, as defined in GVP Module VI, refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised product information. Misuse for illegal purposes has the additional connotation of an intention of misusing the medicinal product to cause an effect in another person. This includes, amongst others: the sale, to other people, of medicines for recreational purposes and use of a medicinal product to facilitate assault. If appropriate, the means of limiting this, e.g. by the use of colorants and/or flavourings in the dosage form, limited pack size and controlled distribution should be discussed in the risk minimisation plan.

V.B.8.6.4. RMP module SVI section “Potential for medication errors”

For the purposes of the RMP, medication error refers to any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use. Medication errors are an important cause of morbidity and mortality and many could be prevented or mitigated. They fall broadly into four categories:

1. Wrong medication
2. Wrong dose (including strength, form, concentration, amount)
3. Wrong route of administration
4. Wrong patient

Applicants/marketing authorisation holders should consider routinely the likelihood of medication errors. In particular, they should assess, prior to marketing, common sources of

medication errors. During the development phase and during the design of a medicinal product for marketing, the applicant needs to take into account potential reasons for medication error. The naming of Invented Names for Human Medicinal Products, presentation (e.g. size, shape and colouring of the pharmaceutical form and packaging), instructions for use (e.g. regarding reconstitution, parenteral routes of administration, dose calculation) and labelling are among the items to be considered. In addition, Guidelines of the Label and Package Leaflet of Medicinal Products for Human Use in the KSA should be followed.

If a product has potential for serious harm when administered by an incorrect route, consideration should be given as to how such administration can be avoided. This is particularly important when it is common practice to administer the product at the same time as other medicinal products given by the hazardous route. In this situation, medication errors should be included as a safety concern.

The need for visual (or physical) differentiation between strengths of the same medicinal product and between other medicinal products commonly administered or taken at the same time should be discussed. In addition, if there are other products containing the same active substance on the market with formulations which are not proven to be bioequivalent, measures to avoid medication error should be discussed and appropriate risk minimisation activities proposed.

When a medicinal product is likely to be used by a visually impaired population, special consideration should be given to the potential for medication error. Where appropriate, medication error should be included as a safety concern and appropriate risk minimisation measures proposed to address the possibility of medication error due to visual impairment. Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

Medication errors 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 taken into account in the final product design.

If during the post-marketing period it becomes apparent that adverse reactions are occurring as a result of medication errors, this topic should be discussed in the updated RMP and ways of limiting the errors proposed.

If the formulation or strength of a product is being changed, where appropriate, medication error should be included as a safety concern and the measures that the marketing authorisation holder will put in place to reduce confusion between old and new “product” should be discussed in the risk minimisation plan. Similarly, it may be appropriate to discuss risk minimisation activities in relation to changes to the presentation, pack size, route of administration or release characteristics of the medicinal product.

If the product is to be administered with a medical device (integrated or not), consideration should be given to any safety concerns which could represent a risk to the patient (medical device malfunction).

V.B.8.6.5. RMP module SVI section “Potential for off-label use”

The potential for off-label use should be discussed. Off-label use relates to situations where the medicinal product is intentionally used for a medical purpose not in accordance with the authorised product information. This is particularly relevant where a medicinal product has an indication restricted to a subset of the population within a disease area or there are situations where the medicinal product must not be given for safety reasons. The potential for use in other disease areas should also be considered where this is likely.

Where appropriate, use could be made of data on actual use versus authorised use in other markets and the implications for the authorisation in the KSA.

V.B.8.6.6. RMP module SVI section “Specific paediatric issues”

This section deals with aspects of paediatric use not covered in RMP module SIV.

Issues identified in paediatric investigation plans

Any recommendations for long term follow up of safety or efficacy issues in relation to paediatric use which are mentioned in the paediatric investigation plan should be detailed here. This section should clarify if, and how, this had been taken into account in RMP module SVII. If the issue has been resolved following further development, or is no longer considered of sufficient impact to justify listing as a safety concern, this should be discussed and justified.

Proposals for specific long term paediatric studies should be considered at the time of application for a paediatric indication and if felt not to be necessary justification should be provided. If an indication in adults precedes an application for paediatric use, any registries established to provide data on use of the product in real medical practice should avoid age related exclusion criteria so that any potential off-label use in the paediatric population can be included.

In some circumstances, the safety concern identified in the paediatric investigation plan may be applicable to the whole population being treated. In these cases, consideration should be given as to whether some of the pharmacovigilance activities and/or risk minimisation activities from the paediatric investigation plan are appropriate for, and should be extended to cover, the whole population. For these safety concerns, this RMP section should also include details of how the specific paediatric aspects will be addressed and all paediatric investigation plan recommendations considered. Cross-reference may be made to RMP modules SIV and SVII and SVII.

Potential for paediatric off-label use

If the disease or disorder which is being treated or prevented is found in the paediatric population, and the product is not authorised in all paediatric age groups, the potential for off-label paediatric use in the non-authorised age groups should be discussed. If there are limited treatment options it should not be assumed that clinicians will adhere to the labelled indication so it is important that potential paediatric issues are discussed. Any actual use should be discussed in RMP module SV section “Non-study post-authorisation exposure” (see V.B.8.5.2.) and in RMP module SV section “Post-authorisation use in populations not studied in clinical trials” (see V.B.8.5.3.).

V.B.8.7. RMP module SVII “Identified and potential risks”

This RMP module provides information on the important identified and potential risks associated with use of the product. These should include only the important identified and potential adverse events/reactions, important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects.

Because of the need for different additional categories of risks to be considered with advanced therapy medicinal products, a different version of RMP module SVII is available for products classified as advanced medicinal products. Only one version (either sections V.B.8.7.1- V.B.8.7.5 or sections V.B.8.8.1 – V.B.8.8.3) of RMP module SVII should be provided in a RMP.

V.B.8.7.1. RMP module SVII section “Newly identified safety concerns”

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of the safety concern should be stated, whether it is an important

identified or important potential risk and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

V.B.8.7.2. RMP module SVII section “Recent study reports with implications for safety concerns”

Study reports (either interim or final, from whichever type of study), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate (eg RMP module SII; section V.B.8.7.3; V.B.8.7.4; V.B.8.7.5; RMP Module SVI and RMP Module SVIII

V.B.8.7.3. RMP module SVII section “Details of important identified and potential risks from clinical development and post-authorisation experience”

This RMP section should provide more information on the important identified and potential risks. This RMP section should be concise and should not be a data dump of tables or lists of adverse reactions from clinical trials, or the proposed or actual contents of section 4.8 of SPC.

What constitutes an important risk will depend upon several factors including the impact on the individual patient, the seriousness of the risk and the impact on public health (see also V.B.1). Normally, any risk which is clinically important and which is/is likely to be included in the contraindications or warnings and precautions section of the SPC should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of the treated population, affect the quality of the treated person’s life, and which could lead to serious consequences if untreated should also be considered for inclusion, e.g. severe nausea and vomiting with chemotherapy.

For some products, disposal of the used product may constitute a safety concern, e.g. transdermal patches where there may be significant amounts of active substance remaining in the patch when it is discarded. There may also be occasions where there is an environmental concern over product disposal because of known harmful effects on the environment, e.g. substances which are particularly hazardous to aquatic life which should not be disposed of in landfill sites.

Presentation of risk data:

When the information is available, detailed risk data should include the following:

- frequency;
- public health impact (severity and seriousness/reversibility/outcomes);
- impact on the individual patient (effect on quality of life);
- risk factors (including patient factors, dose, at risk period, additive or synergistic factors);
- preventability (i.e. predictability of a risk, whether risk factors have been identified, or possibility of detection at an early stage which could mitigate seriousness);
- potential mechanism;
- evidence source(s) and strength of the evidence.

The frequency of important identified risks should be expressed taking into account the source of the data. For a product already on the market, the reporting rate based on the number of spontaneously reported adverse events/adverse reactions (in the numerator) and the sales data (in the denominator) is very likely to underestimate the rate of occurrence of an adverse reaction in an exposed population and should be avoided. When an accurate frequency is needed for an important identified risk, this should always be based on systematic studies (e.g. clinical trials or epidemiological studies) in which both the number

of patients exposed to the medicinal product and the number of patients who experienced the respective identified risk are known.

The denominator should be expressed using the appropriate measure: e.g. number of patients or in patient-time or equivalent units (courses of treatment, prescriptions, etc.) It should be stated clearly which frequency parameter is being used: e.g. incidence proportion (patient units in the denominator) or incidence rate (patient-time units in the denominator). Confidence intervals should be provided. When using patient-time, the underlying assumption is that the hazard function must be nearly constant over the follow-up time. Otherwise it should be split into relevant categories where the assumption of constancy holds. This may be particularly important if treatment duration is a risk factor. Where appropriate, the period of major risk should be identified. Identified risk incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess (relative incidence compared to a specified comparator group) should be given. Time to event data should be summarised using survival techniques. Cumulative hazard functions may also be used to represent the cumulative probability of occurrence of an adverse reaction in the presence of competing events.

For potential risks, the background incidence/prevalence in the target population(s) should be provided.

For most RMPs involving single products, risks which relate specifically to an indication or formulation can usually be handled as individual safety concerns, e.g. accidental IV administration could be a safety concern in a single product with both oral and subcutaneous forms.

For RMPs covering multiple products where there may be significant differences in the identified and potential risks for different products, it may be appropriate to categorise the risks to make it clearer which risks relate to which product. Headings which could be considered include:

- Risks relating to the active substance

This would include important identified or potential risks which are common to all formulations, routes of administration and target populations. It is likely that most risks will fall into this category for the majority of products.

- Risks related to a specific formulation or route of administration

Examples might include an RMP with two products: one a depot intramuscular formulation and the other an oral formulation. Additional concerns relating to accidental intravenous administration clearly would not be applicable to the oral product.

- Risks relating to a specific target population

The paediatric population is an obvious example of a target population where there may be additional risks relating to physical, mental and sexual development which would not be relevant to a product intended solely for adult patients.

- Risks associated with switch to non-prescription status.

Division of identified and potential risks using headings should only be considered when the risks clearly do not apply to some products and lack of separation could cause confusion.

V.B.8.7.4. RMP module SVII section “Identified and potential interactions including food-drug and drug-drug interactions”

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed in relation to both the treatments for the condition, but also in relation to

commonly used medications in the target population. For each, the evidence supporting the interaction and possible mechanism should be summarised, and the potential health risks posed for the different indications and in the different populations should be discussed. Interactions which are important clinically should be included as a safety concern in RMP module SVIII “Summary of the safety concerns.”

V.B.8.7.5. RMP module SVII section “Pharmacological class effects”

Important risks which have not been included in RMP module SVII “Details of important identified and potential risks from clinical development and post-authorisation experience” (above) but which are believed to be common to the pharmacological class should be discussed here. The discussion should include the mechanism, the impact (severity and duration), frequency seen with other members of the same or similar pharmacological class. For risks which have been included in the RMP section SVII “*Details of important and identified and potential risks from clinical development and post-authorisation experience*” (above), all that is required in this RMP section are the frequencies seen with the medicinal product compared with those seen with other products in the same or similar pharmacological class.

If there is evidence that a risk, which is common to other members of the pharmacological class, is not thought to be a safety concern with the concerned medicinal product, details, and the evidence supporting this, should be provided and discussed.

V.B.8.8. RMP module SVII “Identified and potential risks (ATMP version)”

Advanced therapy medicinal products (ATMPs) because of their nature may have specific risks that are usually not applicable to other non-advanced therapy medicinal products. (see guideline: EMA Guideline on Safety and Efficacy Follow-up – Risk Management of

Advanced Therapy Medicinal Products)³ For this reason, for ATMPs, this ATMP specific version of RMP module replaces the standard RMP module SVII.

Although not all of the risks listed in section V.B.8.8.3. are unique to ATMPs or applicable to all ATMPs, they represent the most relevant ones which need to be considered.

V.B.8.8.1. RMP module SVII section “Newly identified safety concerns (ATMP)”

Safety concerns (important identified and important potential risks) identified since the last submission of the RMP should be listed here and further discussed in the appropriate section below. The source of the safety concern should be stated, whether it is an important identified or important potential risk and whether new studies or risk minimisation activities are proposed (with further details in the appropriate RMP parts).

V.B.8.8.2. RMP module SVII section “Recent study reports with implications for safety concerns (ATMP)”

Study reports (either interim or final), since the last RMP, which contain results which have a significant impact on an existing safety concern should be discussed here. The conclusions should be incorporated into the other sections of the safety specification as appropriate (e.g. RMP module SII; section V.B.8.8.3; RMP Module SVI and RMP Module SVIII

V.B.8.8.3. RMP module SVII section “Details of important identified and potential risks (ATMP)”

This section should provide more information on the most important identified and potential risks. This section should be selective and should not be a data dump of tables or

³http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf

lists of adverse reactions from clinical trials, or the proposed or actual contents of section 4.8 of the SPC.

What constitutes an important risk will depend upon several factors including the impact on the individual, the seriousness of the risk and the impact on public health. Normally, any risk which is clinically important and is/is likely to be included in the warnings and precautions section of the SPC should be included here. In addition, risks, which, whilst not normally serious enough to require specific warnings or precautions but which occur in a significant proportion of either the patient or donor, affect the quality of life, and which could lead to serious consequences if untreated should also be considered for inclusion. The additional risks specific to ATMPs which should be considered for discussion include:

- risks to living donors, for instance:
 - risks to living donors related to their conditioning prior to procurement (e.g. immunosuppression, cytotoxic agents, growth factors);
 - risks to living donors related to surgical/medical procedures used during or following procurement, irrespective of whether the tissue was collected or not;
- risks to patients related to quality characteristics of the product, in particular:
 - species of origin and characteristics of cells (and related body fluids, biomaterials, biomolecules) that are used during manufacturing, and the safety testing performed;
 - characteristics of vectors for gene therapy medicinal products;
 - biologically active substances used in manufacturing (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
 - quality assurance and characteristics of the finished product in terms of defined composition, stability, biological activity, and purity with reference to non-physiologic proteins and fragments thereof;

- risk related to transmissible diseases (e.g. viral, bacterial, parasitical infections and infestations, but also malignant disease);
- risks to patients related to the storage and distribution of the product, for instance:
 - risks related to preservation, freezing and thawing;
 - risks of breaking the cold chain or other type of controlled temperature conditions;
 - risks related to stability of the product;
- risks to patients related to administration procedures, for instance:
 - biologically active substances used in preparation of the product prior to administration (e.g. enzymes, antibodies, cytokines, sera, growth factors, antibiotics);
 - risks related to conditioning of the patient;
 - risks of related medical or surgical procedures (e.g. anaesthesia, infusion, transfusion, implantation, transplantation or other application method);
 - risks related to clinical follow-up (e.g. immunosuppression as co-medication or as necessary for treatment of complications, diagnostic procedures, hospitalisation);
 - risks related to mistakes or violations of the standard procedures for administration of the product (e.g. different administration procedures used by different healthcare establishments/healthcare professionals resulting in differing results);
- risks related to interaction of the product and the patient, for instance:
 - unwanted immunogenicity and its consequences (including e.g. anaphylaxis, graft versus host disease, graft rejection, hypersensitivity reactions, immune deficiencies);
 - risks related to both intended and unintended genetic modification of the patient's cells (apoptosis, change of function, alteration of growth and/or differentiation, malignancy);
 - early and late consequences of homing, grafting, differentiation, migration and proliferation;

- risks related to infection with vectors used in gene therapy medicinal products (type of vector, target cells, persistence, potential for latency and reactivation, potential for integration of genetic material into the host genome, prolonged expression of the transgene, altered expression of the host's genes);
- risks related to scaffolds, matrices and biomaterials (e.g. biodegradation, mechanical factors);
- risks related to persistence of the product in the patient, e.g.:
 - availability of rescue procedures or antidotes and their risks;
 - late complications, particularly malignancies and auto-immunity;
 - considerations on the potential impact of previous, concomitant, or future therapies typical for the diagnosis or treatment of the respective disease on the product, or vice versa impact of the product on those other therapies (e.g. an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction);
- risks related to re-administration, for instance:
 - immune reactions - anaphylaxis, neutralising antibodies;
 - risks related to repeated surgical or administration procedures;
- risks to close contacts, for instance:
 - based on the environmental risk assessment, virus shedding and its consequences;
- specific parent-child risks, for instance:
 - risk of germ line integration of transgene, or other genetic transformation of the germ line;
 - foetal transmission (of e.g. vectors, biologically active substances, cells, infectious agents);

– trans-mammary exposure of children in breast-feeding women (to e.g. vectors, biologically active substances, cells, infectious agents).

V.B.8.9. RMP module SVIII “Summary of the safety concerns”

At the end of the safety specification a summary should be provided of the safety concerns.

A safety concern may be an:

- important identified risk;
- important potential risk; or
- missing information.

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

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

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

V.B.9. RMP Part III “Pharmacovigilance plan”

The purpose of the pharmacovigilance plan is to discuss how the applicant/marketing authorisation holder plans to identify and/or characterise the risks identified in the safety specification. It provides a structured plan for:

- the identification of new safety concerns;
- further characterisation of known safety concerns including elucidation of risk factors;
- the investigation of whether a potential safety concern is real or not;
- how missing information will be sought.

It does NOT include actions intended to reduce, prevent or mitigate risks

The pharmacovigilance plan should be based on the safety concerns summarised in RMP module SVIII of the safety specification. Early discussions SFDA and the marketing authorisation holder or applicant are recommended to identify whether, and which, additional pharmacovigilance activities are needed. It is important to note that only a proportion of risks are likely to be foreseeable and therefore signal detection, which is part of routine pharmacovigilance, will be an important element in identifying new risks for all products.

Pharmacovigilance activities can be divided into routine pharmacovigilance activities and additional pharmacovigilance activities. For each safety concern, the applicant/marketing authorisation holder should list their planned pharmacovigilance activities for that concern. Pharmacovigilance plans should be proportionate to the risks of the product. If routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies) “routine pharmacovigilance” should be entered against the safety concern.

V.B.9.1. RMP part III section “Routine pharmacovigilance activities”

Routine pharmacovigilance is the set of activities required to fulfil the legal requirements for pharmacovigilance contained within the national pharmacovigilance regulations in the KSA. The Pharmacovigilance System Master File contains details of the system and processes each marketing authorisation applicant/holder has in place to achieve this. These details are not required to be submitted in the RMP.

In certain situations, 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 Module I). If these recommendations include recording of tests (including in a structured format) which would form part of normal clinical practice for a patient experiencing the adverse reaction then this requirement would still be considered as 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 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) which is outside “normal” clinical practice, then this would constitute an additional PhV activity.

Specific adverse reaction follow-up questionnaires

Where an applicant/marketing authorisation holder is requested, or plans to use, specific questionnaires to obtain structured information on reported adverse reactions of special interest, copies of these forms should be provided in RMP annex 7 and will be made available upon request. Applicants/marketing authorisation holders are encouraged to use the same or similar questionnaires for the same adverse event to decrease the burden on healthcare professionals.

Use of specific questionnaires as a follow-up to a reported suspected adverse reaction is considered to be routine pharmacovigilance.

V.B.9.2. RMP part III section “Additional pharmacovigilance activities”

Additional Pharmacovigilance activities may be non-clinical studies, clinical trials or non-interventional studies. A safety concern may have no, or a number of, additional pharmacovigilance activities associated with it depending upon its nature, the degree to which it has already been characterised, and the feasibility of studying it. Applicants/marketing authorisation holders should consider the situations when additional pharmacovigilance activities are needed. For example, a medicinal product intended for chronic use may only have relatively short term follow up data at the time of authorisation. Long term follow-up of patients from the clinical trial population or a cohort study may provide additional reassurance on the long term effects of the medicinal product. A medicinal product, where there is conflicting pre-clinical data, e.g. carcinogenicity in only one species, may also require long term follow-up of a cohort of patients to confirm that there is not an increased risk of cancer in human use. Another example, when additional pharmacovigilance activities should be considered, is when a potential risk with an individual medicinal product has a significant background incidence in the target population(s), leading to difficulties in distinguishing between the effects of the medicinal product and the “normal” incidence. When any doubt exists about the need for additional pharmacovigilance activities, consultation with the SFDA should be considered.

The objective(s) of additional pharmacovigilance activities will normally differ according to the safety concern to be addressed. For important identified and potential risks, objectives may be to measure the incidence rate in a larger or a different population, to measure the rate ratio or rate difference in comparison to a reference medicinal product, to examine how the risk varies with different doses and durations of exposure, to identify risk factors or to assess a causal association. For missing information, the objective may simply be to investigate the possibility of a risk or to provide reassurance about the absence of a risk.

The threshold for investigating a safety concern further will depend upon the indication, the target population, and the likely impact on public health. For example, a safety concern

with a vaccine might have a lower threshold for investigation than the same issue in a medicinal product used in the palliative treatment of metastatic cancer.

Studies in the pharmacovigilance plan should relate to the safety concerns identified in the safety specification whether the studies are to identify and characterise risks, or to assess the effectiveness of risk minimisation activities. The applicant/marketing authorisation holder should include all studies designed to address the safety concern or measure the effectiveness of risk minimisation measures. This includes all post-authorisation safety studies which are initiated, managed or financed by marketing authorisation holders, voluntarily, or pursuant to obligations imposed by SFDA. Studies requested by other regulatory authorities to investigate a specific safety concern should also be included. If a marketing authorisation applicant/holder has a marketing partner, studies designed to address a particular safety concern which are initiated, managed or financed by that partner should be included in the pharmacovigilance plan, if possible.

If, when reviewing a study protocol, a study is thought not to have as its primary focus one of the objectives of a post-authorisation safety studies (PASS) (as described in Module VIII), or a post-authorisation efficacy studies (PAES), or the study is judged to be unlikely to achieve its stated scientific purpose, the applicant/marketing authorisation holder will be required to modify it or remove it from the pharmacovigilance plan and resubmit the RMP.

Pharmacoepidemiology studies included in the pharmacovigilance plan should be designed and conducted according to the respective legislation in place and recommendations in the [Guidelines for Good Pharmacoepidemiology Practices (GPP)⁴ and the ENCePP Guide on

⁴ International Society for Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practices (GPP).

Pharmacoepidemiol Drug Saf. 2005; 14 (8): 589-595; available on the ISPE website

http://www.pharmacoepi.org/resources/guidelines_08027.cfm

Methodological Standards in Pharmacoepidemiology⁵. For studies involving children, refer to the EMA Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population⁶]. It is highly recommended that expert advice is sought on the design and conduct of any studies – whether by the scientific advice procedure or by consulting known experts in the appropriate field. The responsibility for the scientific value of study protocols remains with applicants or marketing authorisation holders, even if they have been previously discussed with the SFDA. Further guidance on the conduct of PASS is given in Module VIII.

For some safety concerns, additional pharmacovigilance activities other than pharmacoepidemiology studies may be required, e.g. pharmacokinetic studies, clinical trials or further pre-clinical work. The appropriate guidelines and legislation should be followed in the conduct of these studies.

Protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until completion of the study and submission to the SFDA of the final study report.

For studies conducted as an obligation, the marketing authorisation holder shall submit the study protocol, in English. For other studies, if the study protocol or the study report is written in another language, the marketing authorisation 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 (see Module VIII.)

Synopses of study reports from additional pharmacovigilance activities should be included in RMP annex 9. The impact of the new data on the benefit-risk profile of the medicinal

⁵ ENCePP Guide on Methodological Standards in Pharmacoepidemiology” EMA/95098/2010; available on <http://www.encepp.eu>

⁶ EMEA/CHMP/PhVWP/235910/2005; available on http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000087.jsp&mid=WC0b01ac0580025b90&jsenabled=true

product should be carefully assessed and the safety specification, pharmacovigilance plan and risk minimisation measures updated accordingly.

V.B.9.2.1. Particular situations with post authorisation safety studies

This section should be read in conjunction with Module VIII – Post authorisation Safety Studies.

a. Studies to measure the effectiveness of risk minimisation measures

Post-authorisation safety studies (PASS) include in their definition studies which measure the effectiveness of risk management measures. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan against the specific safety concern(s) as well as described in detail in the risk minimisation plan. Further guidance on measuring the effectiveness of risk minimisation measures can be found in GVP Module XVI

b. Drug utilisation studies

Drug utilisation studies are sometimes requested by the SFDA to monitor drug usage in the KSA. often in relation to reimbursement discussions. However, although they may not be initiated to collect safety data, they can provide useful information on whether risk minimisation activities are effective and on the demographics of target populations. Ideally, requests for drug utilisation studies by the SFDA or any country worldwide should be included in the pharmacovigilance plan. However, these studies are sometimes requested post-authorisation by authorities not involved in medicinal product licensing. In these circumstances, the studies should be included in the next update to the RMP.

c. Joint studies

If safety concerns apply to more than one medicinal product, the SFDA shall, sometimes following consultation with the Saudi pharmacovigilance Advisory committee, encourage the marketing authorisation holders concerned to conduct a joint PASS. The conduct of a joint study may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. SFDA should facilitate the agreement of the concerned marketing authorisation holders in developing a single protocol for the study and conducting the study. If, within a reasonable period of time, as determined by the SFDA, the concerned marketing authorisation holders have failed to agree a common protocol the SFDA may impose a PASS and define either a common core protocol or key elements within a protocol which the concerned marketing authorisation holders will have to implement within a timescale laid down within the request. Hence, the study would become a condition of the marketing authorisation and be reflected in the RMP.

In some circumstances, the requirement to do joint studies may relate to a single active substance where there are multiple marketing authorisation holders for the same active substance.

d. Registries

A registry is an organised 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 (disease registry) or prescription of a drug (exposure registry)

Registries should ideally include a comparator group so a disease registry will usually be more suitable than a registry confined to a specific product. However, if, an applicant/marketing authorisation holder institutes a registry as part of an agreed RMP, the protocol for the registry will allow all patients who are prescribed the active substance or

who have the same disease, as appropriate, to be entered in the registry. Entry to the registry should not be conditional on being prescribed a product with a particular invented name or marketing authorisation holder unless there are clear scientific reasons for this. The same applies to similar biological products.

Unless there are over-riding public health or scientific concerns which lead to mandatory inclusion in a registry, refusal to enter a registry should not normally be a reason for refusing access to a medicine.

V.B.9.3. RMP part III section “Action plans for safety concerns with additional pharmacovigilance requirements”

For safety concerns with additional pharmacovigilance activities only, the action plan for each safety concern should be presented according to the following structure:

- safety concern;
- proposed action(s);
- individual objectives of proposed action(s) (ie what aspects of the safety concern they are intended to characterise);

For each action:

- details of individual action
 - steps
 - milestones (including expected dates)

As well as listing any additional pharmacovigilance activities under “proposed actions,” protocols (draft or otherwise) for any formal studies should be provided in RMP annex 6. Marketing authorisation applicants/holders should also follow the requirements detailed in

Module VIII, where appropriate. It is recommended that the ENCePP Guide on Methodological Standards in Pharmacoepidemiology⁹ including the ENCePP Checklist for Study Protocols¹⁰, should be referred to when considering epidemiological protocol design.

V.B.9.4. RMP part III section “Summary table of additional pharmacovigilance activities”

The pharmacovigilance plan describes pharmacovigilance activities designed to identify and characterise risks associated with the use of a medicinal product. Some may be imposed as conditions of the marketing authorisation (MA) either because they are key to the benefit-risk of the product, or because they are specific obligations in the context of a MA under exceptional circumstances.⁷

The pharmacovigilance plan also includes studies that are conducted or financed by the marketing authorisation holder to address particular safety concerns and so includes studies which are not obligations in the above sense. These studies may be on-going or planned, may have been requested by another regulatory authority, may have been specifically requested by the SFDA or may have been suggested by the marketing authorisation applicant/holder and agreed with the SFDA as forming part of the pharmacovigilance plan. They may also be conducted to evaluate the effectiveness of risk minimisation activities. Finally, the Pharmacovigilance Plan also has a role in providing an overview of studies which, although not part of the formal agreed plan to identify and characterise specific safety concerns, the Rapporteur, Reference Member State or SFDA needs to be aware of. These studies are typically requested post-authorisation by the SFDA for reimbursement reasons e.g. drug utilisation studies.

⁷ Exceptional circumstances is a type of marketing authorisation granted to medicines where the applicant is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because the condition to be treated is rare or because collection of full information is not possible or is unethical.

The summary table of the pharmacovigilance plan should provide clarity to all stakeholders as to which category an activity in the pharmacovigilance plan falls under, i.e.:

- 1) Specific Obligations in the framework of a MA under exceptional circumstances. These studies will also be reflected in Annex II to the marketing authorisation (or national equivalent).
- 2) Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities
- 3) Other studies conducted by MAH which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimisation activities.

Table V.2: Attributes of different PhV activities

	Type of activity	Category in Summary table of PhV activities	Status
Imposed PASS	“Interventional”*	1	Mandatory and subject to penalties
	Non-interventional	1	Mandatory and subject to penalties
Specific obligation	“Interventional”*	2	Mandatory and subject to penalties

	Non-interventional	2	Mandatory and subject to penalties
Required	“interventional”*	3	enforceable
	Non-interventional	3	enforceable
Stated	“interventional”*	4	Not enforced
	Non-interventional	4	Not enforced

*Clinical interventional studies are subject to the requirements of national regulations in the KSA. Non-clinical interventional studies are subject to the legal and ethical requirements related to the protection of laboratory animals, and Good Laboratory Practice as appropriate.

For activities in categories 1-3, the following summary table should be used:

Description of Activity	Milestones <i>(may be several per activity)</i>	Due Date <i>(may be several per activity)</i>

For activities in category 4 the following summary table should be used:

Description of Activity	Expected date when results will be available

V.B.10. RMP part IV “Plans for post-authorisation efficacy studies”

Efficacy, as assessed at the time of authorisation, is based on data from clinical trials which, by their nature, are of relatively limited duration (e.g. usually between 6 months – 3 years). The benefit (efficacy of the medicine) risk balance must be positive for a medicine to be authorised. Whereas it is recognised that many risks will be identified post authorisation, there is an implicit assumption that efficacy remains relatively constant over time. This may not always be valid.

For most medicines there will not be a need for post-authorisation efficacy studies. However, there may be circumstances where efficacy may vary over time and also patients in whom this assumption of constant efficacy may not be true and where longer term efficacy data post authorisation is necessary.

For regulations on paediatric medicinal products and advanced therapy medicinal products. There is a need for long term follow-up of efficacy as part of post-authorisation surveillance for certain medicinal products namely:

- applications for a marketing authorisation that include a paediatric indication;
- applications to add a paediatric indication to an existing marketing authorisation;
- application for a paediatric use marketing authorisation;

- advanced therapy medicinal products.

In addition, the SFDA may require PAES for products where there are concerns about efficacy which can only be resolved after the product has been marketed, or when knowledge about the disease or the clinical methodology used to investigate efficacy indicate that previous efficacy evaluations may need significant revision. Although the guidelines refer to the studies as PAES, the fact that these efficacy issues can only be resolved post-authorisation implies that this term includes effectiveness studies.

The requirement for efficacy studies post authorisation refers solely to the current indication(s) and not to studies investigating additional indications.

V.B.10.1. RMP part IV section “Summary of existing efficacy data”

As background to any proposed post-authorisation efficacy studies, and to provide context for the summary of the RMP, there should be a summary of the efficacy of the product and the studies and endpoints on which it was based. Where the RMP covers more than one medicinal product, the information should be provided by medicinal product to permit easy extraction for the summary of the RMP module. Similarly medicinal products with more than one indication should have a separate summary of efficacy for each one.

The summary of efficacy (one page maximum per indication/population) should be in lay language and the following should be considered for inclusion:

- current (gold) standards of treatment
- where the medicinal product fits in the therapeutic armamentarium (ie 1st line, relapse etc)
- a brief statement of the standard against which the medicine was judged
- number of patients in pivotal studies and treatment regimes

- results in lay language

The following areas should be discussed briefly and the need for further studies post authorisation evaluated:

- the robustness of the endpoints on which the efficacy evaluation is based
- applicability of the efficacy data to all patients in the target population;
- factors which might affect the efficacy of the product in everyday medical practice;
- variability in benefits of treatment for sub populations.

For updates to the RMP, any subsequent data which impacts on efficacy should be mentioned and its impact on the benefits of the medicinal product discussed.

V.B.10.2 Tables of post-authorisation efficacy studies

A summary table showing an overview of the planned studies together with timelines and milestones should be provided here with the (draft) protocols for these studies included in RMP annex 8.

Efficacy studies which are specific obligations and/or conditions of the marketing authorisation should also be included in this part of the RMP.

Efficacy studies which are specific obligations and/or conditions of the MA

Description of Study	Milestones <i>(may be several Per activity)</i>	Due Date <i>(may be several Per activity)</i>

Other efficacy/effectiveness studies

Description of Study	Milestones <i>(may be several Per activity)</i>	Due Date <i>(may be several Per activity)</i>

V.B.11. RMP Part V “Risk minimisation measures”

On the basis of the safety specification, a marketing authorisation applicant/holder should assess what risk minimisation activities are needed for each safety concern. The risk minimisation plan should provide details of the risk minimisation measures which will be taken to reduce the risks associated with individual safety concerns. It is not possible to provide precise guidance on which risk minimisation activity should be used in a given situation as each safety concern needs to be considered on a case-by-case basis and will depend upon the severity of the risk, the healthcare setting, the indication, the pharmaceutical form and the target population. A safety concern may be addressed using more than one risk minimisation measure.

For active substances where there are individual products with substantially different indications or target populations, it may be appropriate to have a risk minimisation plan specific to each product. Examples when multiple risk minimisation plans could be considered include:

- an active substance where there are products with both prescription only and non-prescription legal status;

- medicinal products where there are major risks, and the indications cross areas of medical expertise. In the latter case, there could be diverse educational needs for different specialists since the areas of specialised knowledge will be distinct. For example an active substance which causes important QT prolongation would most likely not need educational material explaining the implications of this and the interactions with other products if the product were intended solely for use by cardiologists in a hospital setting but might need educational material if intended for use in general practice or orthopaedic surgery where it is unlikely that prescribers will have this specialist knowledge;
- active substances where there are major risks which differ according to the target population.

Risk minimisation activities may consist of routine risk minimisation (e.g. measures associated with locally authorised product labelling) or additional risk minimisation activities (e.g. Dear Healthcare Professional Communications/educational materials/controlled distribution systems). All risk minimisation measures should have a clearly identifiable objective.

All risk minimisation measures should be reviewed at regular intervals and their effectiveness assessed (see V.B.11.4).

Additional risk minimisation measures and the assessment of the effectiveness of risk minimisation measures in general is discussed in more detail in Module XVI.

V.B.11.1. RMP part V section “Routine risk minimisation”

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

These relate to:

- the summary of product characteristics;
- the labelling;

- the package leaflet;
- the pack size(s);
- the legal status of the product.

The summary of product characteristics (SPC) and the package leaflet are important tools for risk minimisation as they constitute a controlled and standardised format for informing healthcare practitioners and patients about the medicinal product. refer to the guideline for “The GCC Guidance for Presenting the SPC, PIL and Labeling Information⁸ to know how information should be presented provides guidance on how information should be presented. As discussed in V.B.8.6.4., the design of the packaging, and even the formulation itself, may play an important role in preventing medication error.

a. Pack size

Since every pack size is specifically authorised 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: 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 is thought to be a major risk or if the potential for drugs to get into the general population needs to be controlled.

b. Legal status

8

http://www.sfda.gov.sa/en/drug/drug_reg/Regulations/Guidance%20for%20SPC%20PIL%20SFDA%20version%202.0.pdf

All medicinal products in the KSA have a legal status. Controlling the conditions under which a medicinal product may be made available can reduce the risks associated with its use or misuse. This can be achieved by controlling the conditions under which a medicinal product may be prescribed, or the conditions under which a patient may receive a medicinal product.

When a marketing authorisation is granted, it must include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which a medicinal product may be made available to patients. The conditions under which a medicinal product is made available is commonly referred to as the “legal status” of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medicinal prescription. It may also restrict where the medicinal product can be administered (e.g. in a hospital, but see below) or by whom it may be prescribed (e.g. specialist).

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

Restricted medical prescription

This may be used to control who may initiate treatment, prescribe the medicinal product and the setting in which the medicine can be given or used. According to the KSA legislation, when considering classification of a medicinal product as subject to restricted medical prescription, the following factors shall be taken into account:

- 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 for 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; or
- the medicinal product is intended for outpatients but its use may produce very serious adverse reactions requiring prescription drawn up as required by a specialist and special supervision throughout the treatment,

Although the use of legal status is not an activity that can be used directly by a marketing authorisation applicant for the purposes of risk reduction, the marketing authorisation applicant could request the SFDA to consider a particular legal status and this is indicated in the SPC.

In practice, the term “specialist” is sometimes phrased in section 4.2 of the SPC as: “treatment by a physician experienced in the treatment of <the disease>”. Although restricting to use in a hospital environment may in practice ensure that the medicinal product is always prescribed by a specialist, this needs to be balanced against the inconvenience to patients if they need to attend a hospital for every prescription. Care also needs to be taken when considering where a medicinal product can be safely administered. For example the term “clinic” has different connotations depending upon the country. For this reason, the type of equipment needed should be specified rather than a location: e.g. “use in a setting where resuscitation equipment is available.”

Special medical prescription

For classification as subject to special medical prescription, the following factors shall be taken into account:

- 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; or

- 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 previous indent as a precautionary measure.

V.B.11.2. RMP part V section “Additional risk minimisation activities”

Additional risk minimisation activities are those risk minimisation measures which are not the routine risk minimisation activities listed above. Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided.

Many additional risk minimisation tools are based on communication which aims to augment the information in the SPC and the PIL. Any communication material should be clearly focused on the risk minimisation goals, and should not be confused or combined with promotional material for marketing campaigns. Further description and guidance on the use of additional risk minimisation activities is provided in Module XVI.

It is essential that appropriate specialists/ experts are involved when developing risk minimisation activities. Marketing authorisation applicants/ holders are also encouraged to discuss risk minimisation plans with the SFDA as early as is feasible when it is likely that specific risk minimisation activities will need to be adapted to the different health care systems.

The SFDA is the body mandated to review RMPs and makes recommendations on their content and on the suitability of proposed pharmacovigilance activities and risk minimisation measures. Additional risk minimisation measures which are agreed by the SFDA will be allowed in the risk minimisation plan and any other activities considered as

not essential for the safe and effective use of the product will need to be removed and an updated RMP submitted before the SFDA Opinion. Additional risk minimisation activities will become then, conditions of the marketing authorisation and the key elements should be detailed in suitable annex of the SFDA Opinion as appropriate Where appropriate, full details of additional risk minimisation activities (including mock ups) should be provided in RMP annexes 10 and 11.

Educational material

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

The SFDA will agree the key elements of what should be included in the educational material and these key elements will become, once agreed by the SFDA, a condition of the marketing authorisation. The final version of the educational material will need to be approved by SFDA to check that the material contains the key elements in an appropriate design and format and is not promotional.

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

Further extensive guidance on additional risk minimisation measures is provided in Module XVI.

V.B.11.3. Format of risk minimisation plan(s)

Each safety concern identified in the summary of the safety specification should be addressed. If no risk minimisation activity is proposed then “none proposed” should be entered against the objective.

For each safety concern, the following information should be provided:

- Objectives of the risk minimisation activities
- routine risk minimisation activities;
- additional risk minimisation activities (if any), individual objectives and justification of why needed;
- how the effectiveness of each (or all) risk minimisation activities will be evaluated in terms of attainment of their stated objectives;
- what the target is for risk minimisation, i.e. what are the criteria for judging success;
- milestones for evaluation and reporting.

For routine risk minimisation activities, the proposed text in the SPC , should be provided along with details of any other routine risk minimisation activities proposed for that safety concern.

V.B.11.4. RMP part V section “Evaluation of the effectiveness of risk minimisation activities”

Risk minimisation measures are public health interventions intended to prevent or reduce the probability of the occurrence of adverse reactions associated with exposure to a medicinal product, or to reduce their severity/impact on the patient should the adverse reactions occur. The terms "risk minimisation measures and risk minimisation activities

are used virtually synonymously in GVP. The success of risk minimisation activities in delivering these objectives needs to be evaluated throughout the lifecycle of a product to ensure that the burden of adverse reactions is minimised and hence the overall benefit-risk profile is optimised.

When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable. Such information may be presented by region, if applicable/relevant. Results of any studies to assess the impact or other formal assessment(s) of risk minimisation activities should be included when available. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation activities. If a particular risk minimisation strategy proves ineffective, or to be causing an excessive or undue burden on patients or the healthcare system then alternative activities need to be put in place. The marketing authorisation holder should always comment on whether additional or different risk minimisation activities are needed for each safety concern.

In certain cases it may be judged that risk minimisation cannot control the risks to the extent possible to ensure a positive risk-benefit balance and that the medicinal product needs to be withdrawn either from the market or restricted to those patients in whom the benefits outweigh the risks.

More extensive guidance on monitoring the effectiveness of risk minimisation activities is included in Module XVI.

V.B.11.5. RMP part V section “Summary of risk minimisation measures”

A table summarising the routine and additional risk minimisation activities by safety concern should be provided.

V.B.12. RMP part VI “Summary of activities in the risk management plan by medicinal product”

A summary of the RMP for each medicinal product shall be made publically available. The summary must include key elements of the RMP with a specific focus on risk minimisation activities. With regard to the safety specification of the medicinal product concerned, it should contain important information on potential and identified risks as well as missing information.

A scientific summary of the RMP This will be known as “the summary of the RMP” and is described in sections V.B.12.1 – V.B.12.7. .

The Summary of the RMP shall be written by the MAA/MAH and will be evaluated during the assessment of the RMP.

Summary **tables** of the RMP showing the safety concerns, the pharmacovigilance plan, plans for post-authorisation efficacy and risk minimisation measures will be included in this section

There may also be a requirement for additional summaries of the RMP to be provided for inclusion in these documents.

V.B.12.1. RMP part VI section “format and content of the summary of the RMP”

This is a scientific summary, written for the lay reader to fulfil the requirements in the legislation. To present a balanced picture, the risks discussed in the RMP should be put into context with the benefits of the medicinal product. Technical terms, scientific abbreviations or acronyms should be avoided or explained in full if deemed necessary.

The summary of the RMP part VI should contain the following information based on RMP modules SI, SVIII and RMP parts IV and V:

- Overview of disease epidemiology

- Summary of treatment benefits;
- Unknowns relating to treatment benefits;
- Summary of safety concerns:
 - Important identified risks;
 - Important potential risks;
 - Missing information;
 - Summary of risk minimisation activities by safety concern
 - Planned post authorisation development plan
 - Studies which are a condition of the marketing authorisation (see sections V.B.9.4 and V.B.10.2)
 - Major Changes to the Risk Management Plan over time

The information provided in each section should be brief, focussed and in accordance with the word limits in the templates.

V.B.12.2. RMP part VI section “Overview of disease epidemiology“

The applicant/marketing authorisation holder should summarise the epidemiology of the disease/condition the medicinal product is intended to treat or prevent (as presented in RMP module SI)

If the product is used in a range of disease severity, this fact should be emphasised and discussed. If success of treatment is measured using survival figures, appropriate emphasis should be given to the fact that, by definition, survival (e.g. 5 year survival) figures relate to historical treatment.

If the product is a diagnostic, product used for anaesthesia or similar usage not associated with a particular disease/condition then this section of the overview may be omitted.

V.B.12.3. RMP part VI section “Summary of treatment benefits”

Cross link/reference to V.B.10.1. RMP part IV section “Summary of existing efficacy data”

V.B.12.4. RMP part VI section ““Unknowns relating to treatment benefits”

This should discuss the applicability of efficacy to all patients in the target population. It should

describe very briefly any relevant parts of the target population where experience is limited and whether efficacy is expected to be different in these people, e.g. factors such as age, sex, race and organ impairment.

V.B.12.5. RMP part VI section “Summary of safety concerns”

This section should briefly describe the safety concerns in suitable language for the general public. It should include the frequency and severity of the safety concern for the important identified risks and their preventability.

Risk	What is Known	Preventability
Risk 1		
Risk 2 etc		

For important potential risks the reason why it is thought to be a potential risk (e.g. toxicology in animal study, known effect in other members of the pharmaceutical class) should be explained together with the uncertainties, e.g. “occurs in other medicinal products in the same class but was not seen in the clinical trials for this medicinal product which studied 3,761 people”.

Risk	What is Known	Preventability
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Risk 1		
Risk 2 etc		

For missing information it should be stated (using the above format as well) that there is no, or insufficient, information regarding the safety concern, the possible relevance to the target population should be highlighted as well as the associated recommendations, e.g. contraindication, use with caution.

V.B.12.6. RMP part VI section “Summary of risk minimisation activities by safety concern”

Details of routine risk minimisation measures will be provided in the published summary by a link to the product information.

For each safety concern which has additional risk minimisation measures, brief details of the measures for that concern should be provided. The objective and rationale for each measure should be stated along with the proposed actions e.g.:

These additional risk minimisation measures are for the following risks:

Blood clots (Thromboembolic events)

Healthcare Professional and patient education

Objective and rationale

Patients and HCPs to understand the risk of occurrence of thromboembolic events and the appropriate management of this risk.

Proposed actions

- HCP educational materials to be provided to prescribing physicians and pharmacists warning about these risks and measures to take
 - Patient booklet will inform patients what the symptoms of thromboembolic events are and the importance of seeking medical help immediately
 - Direct HCP communication prior to launch ('Dear HCP' letter).
-

Where there are safety concerns specific to a particular indication or population, or where an ATMP is involved it may be appropriate to structure the risks by the headings suggested in module SVII

V.B.12.7. RMP part VI section “Planned post-authorisation development plan”

Data should be presented in the form of a table showing the planned activities in terms of efficacy studies and the further investigation of safety concerns. This table would combine the data from sections V.B.9.4. and V.B.10.2. Each row of the table should include the name of the study, objectives for the study, the safety concern or efficacy issue being addressed, the status and planned date for submission of the results.

Study	Objectives	Safety efficacy concerns/issue addressed	Status	Planned date for submission of (interim and) final results
Study 1				
Study 2 etc				

Studies which are a condition of the marketing authorisation

Statement on which studies in the above table are conditions of the MA e.g. “None of the above studies is a condition of the marketing authorisation.”

V.B.12.8. RMP part VI section” Summary of changes to the risk management plan over time”

The following table should summarise the activities of the RMP for each medicinal product included; i.e.it should be organised in terms of the actions/activities to be undertaken. The reason for this is that one proposed activity (e.g. a prospective safety cohort study) could address more than one of the safety concerns.

All the activities of the following types should be covered:

the routine pharmacovigilance activities,

the ongoing &planned additional pharmacovigilance activities,

the ongoing &planned post authorisation efficacy studies

the routine risk minimisation measures

the additional risk minimisation measures

Activity name	Type of activity	Addressed safety concern (s)

V.B.12.8. RMP part VI section “Summary of changes to the risk management plan over time”

This table should provide a listing of all significant changes to the RMP in chronological order. This should include, for example, the date and version number of the RMP when new safety concerns were added or existing ones removed or changed, dates and version of the RMP when new studies were added or finished, and a brief summary of changes to risk minimisation activities and the associated dates these changes were agreed. Since changes to risk minimisation activities involve a variation, the date used for changes to risk minimisation activities should be that of the decision by SFDA. The date for safety concerns and studies should be the date of the RMP in which they are first added.

V.B.13. RMP part VII “Annexes to the risk management”

The RMP should contain the annexes listed below. Annexes 1-3, 10 and 11 should be provided for each medicinal product within the RMP. If no information is available for a given annex this should be stated. If a single study is addressing issues in both parts III and IV of the RMP, it should be included in RMP annex 6 with a cross reference in RMP annex 8.

RMP annex 1: Interface between RMP and National Pharmacovigilance and Drug Safety Center

(electronic only)

See <http://www.sfda.gov.sa/en/Pages/default.aspx>

RMP annex 2 SPC and PIL.

RMP annex 3: worldwide marketing authorisation status by country. This should include:

current licence status (approved/refused/ under review/ suspended/expired/withdrawn)

- date(s) of approval/refusal/suspension/expiration/withdrawal,
- date(s) marketed/withdrawn from market
- trade name(s)
- any explanatory comments.

RMP annex 4: Synopsis of on-going and completed clinical trial programme

RMP annex 5: Synopsis of on-going and completed pharmacoepidemiological study programme

RMP annex 6: Protocols for proposed and on-going studies in categories 1-3 of the section “Summary table of additional pharmacovigilance activities” in RMP part III

RMP annex 7: Specific adverse event follow-up forms

RMP annex 8: Protocols for proposed and on-going studies in RMP part IV

RMP annex 9: Synopsis of newly available study reports for RMP parts III-IV

RMP annex 10: Details of proposed additional risk minimisation activities (if applicable)

RMP annex 11: Mock up examples in English for Health Care Providers and Arabic for public of the material provided to healthcare professionals and patients as a requirement of Annex II of the Commission Decision or as a requirement of national authorisations including those using the mutual recognition or decentralised procedure as applicable.

RMP annex 12: Other supporting data (including referenced material)

V.B.14. The relationship between the risk management plan and the periodic safety update report

The primary post-authorisation pharmacovigilance documents will be the RMP and the periodic safety update report (PSUR). 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 is integrated, post-authorisation risk benefit assessment whilst that of the RMP is pre-and post-authorisation risk-benefit management and planning. As such the two documents are complementary. Regarding submission, whereas for many medicinal products, both documents will need to be submitted, for other medicinal products only one will be required depending upon where the product is in its lifecycle. For this reason both documents need to be “stand-alone” but it is anticipated that certain modules may be common to prevent duplication of effort.

The PSUR examines the overall safety profile as part of an integrated benefit-risk evaluation of the medicinal product at set time periods and as such will consider the overall benefit risk profile of the medicinal product (and a much wider range of (suspected) adverse reactions). It is anticipated that only a small proportion of these would be classified as important identified or important potential risks and become a safety concern discussed within the RMP. Deciding to add an adverse reaction to section 4.8 of the SPC is not a sufficient cause per se to include it as a safety concern in the RMP (see V.B.8.7.2.).

When a PSUR and a RMP are to be submitted together, the RMP should reflect the conclusions of the accompanying PSUR. For example if a new signal is discussed in the PSUR and the PSUR concludes that this is an important identified or important potential risk, this risk should be included as a safety concern in the updated RMP submitted with the PSUR. The pharmacovigilance plan and the risk minimisation plan should be updated to reflect the marketing authorisation holder’s proposals to further investigate the safety concern and minimise the risk.

V.B.14.1. Common modules between periodic safety update report and risk management plan

The proposed PSUR and RMP modular format is intended to minimise duplication by enabling common (sections of) modules to be utilised interchangeably across both reports. Common (sections of) modules are identified in the following table.

Table V.3: Common sections between RMP and PSUR (may not be in identical format)

RMP section	PSUR section
Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”	Section 3 – “Actions taken in the reporting interval for safety reasons”
Part II, module SV – “Post-authorisation experience”, section “Non-study post-authorisation 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 – “Characterisation 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 reporting interval)	Sub-section 16.1 – “Summary of safety concerns”

Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”	Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”
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V.B.15. Principles for assessment of risk management plans

The principle points which need to be considered when preparing or reviewing a risk management plan for a medicinal product are:

a. Safety specification

- Have all appropriate parts of the safety specification been included?
- Have all appropriate data been reviewed when compiling the safety specification, i.e. are there important (outstanding) issues from other sections of the dossier which have not been discussed in the safety specification?
- If parts of the target population have not been studied, have appropriate safety concerns in relation to potential risks and missing information been included?
- What are the limitations of the safety database and what reassurance does it provide regarding the safety profile of the medicinal product?
- Are there specific risks in addition to those addressed under ICH-E2E, e.g. off-label use, misuse and abuse, transmission of infectious disease, medication error etc?
- Does the safety specification provide a true reflection of the safety concerns (i.e. important identified risks, important potential risks and missing information) with the product?

- If a generic or hybrid application, have all safety concerns from the reference medicinal product been included in the safety specification?
- Does its place in the therapeutic armamentarium as described concur with the intended indication and current medical practice?

b. Pharmacovigilance plan

- Are all safety concerns from the safety specification covered in the pharmacovigilance plan?
- Are routine pharmacovigilance activities adequate or are additional pharmacovigilance activities necessary?
- Are the activities in the pharmacovigilance plan clearly defined and described and suitable for identifying or characterising risks or providing missing information?
- Are the safety studies which have been imposed by a competent authority as conditions clearly identified?
- If medication error is a safety concern, does the RMP include appropriate proposals to monitor these?
- Are the proposed additional studies necessary and/or useful?
- When draft protocols are provided, are the proposed studies in the pharmacovigilance plan adequate to address the scientific questions and are the studies feasible?
- Are appropriate timelines and milestones defined for the proposed actions, the submission of their results and the updating of the pharmacovigilance plan?

c. Plans for post-authorisation studies on efficacy

- Does the description of the efficacy of the product and what studies and endpoints it was based on conform with the contents of the dossier?
- Do all proposed studies have a valid scientific question as their primary aim and are any designed to increase use of the product)?

d. Risk minimisation measures

- Does the product information adequately reflect all important identified risks and missing information?
- Are any potential risks sufficiently relevant to the safe and effective use of the product that information about them should be included in the product information?
- Is the proposed wording about the risks and location in the product information appropriate and in line with relevant guidelines (e.g. SPC guideline)?
- Has the marketing authorisation holder considered ways to reduce medication errors?
- Has this been translated into appropriate product information (including device design where appropriate) and pack design?
- Are proposed risk minimisation activities appropriate and adequate?
- Have additional risk minimisation activities been suggested and if so, are they risk proportionate and adequately justified?
- Are the methodologies for measuring and assessing the effectiveness of risk minimisation activities well described and appropriate?
- Have criteria for evaluating the success of additional risk minimisation activities been defined a priori?

e. Summary of the Risk Management Plan

- Is it a true representation of the RMP?
- Have the facts been presented appropriately
- Is the content, format and language suitable for the intended audience?
- Have all required formats been provided?

f. When an update is being assessed

- Have new data been incorporated into the safety specification?
- Have appropriate changes been made to the pharmacovigilance plan (if necessary in the light of new data)?
- Is there an evaluation of the effectiveness of risk minimisation measures?
- Have appropriate changes to risk minimisation measures been proposed if necessary?
- Does the new data suggest that a formal evaluation of the risk-benefit balance (if not already done in a PSUR) is needed?

V.B.16. 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 authorisation applicant/holder. As such the qualified person responsible for pharmacovigilance (QPPV) in the KSA should be aware of, and have sufficient authority over the content. The marketing authorisation holder is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in Module I. The marketing authorisation holder should maintain records of when RMPs were submitted to

the SFDA and the significant changes between each version of the RMP. These records, the RMPs and any documents relating to information within the RMP may be subject to audit and inspection by appropriately qualified pharmacovigilance inspectors.

V.C. Operation within KSA

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

V.C.1. Risk management in the KSA

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

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

V.C.2 Situations when a risk management plan should be submitted

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

Requires that for all new marketing applications: the risk management plan describing the risk management system which the applicant will introduce for the medicinal product concerned shall be submitted, together with a summary thereof.

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

- with an application involving a significant change to an existing marketing authorisation:
 - new dosage form;
 - new route of administration;
 - new manufacturing process of a biotechnologically-derived product;
 - paediatric indication;
 - other significant change in indication;

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

- at the request of the SFDA when there is a concern about a risk affecting the risk-benefit balance;
- at the time of the renewal of the marketing authorisation if the product has an existing risk management plan.

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

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

V.C.2.1. Requirements in specific situations

Normally all parts of an RMP should be submitted. However, in certain circumstances as detailed below, in line with the concept of proportionality, certain parts or modules may be omitted (see Figure V.3) unless otherwise requested by the SFDA. However, any safety concerns identified in a reference medicinal product in a module which is omitted from the risk management plan of a generic should be included in RMP module SVIII unless clearly no longer relevant.

Please note that the naming and numbering of the RMP parts, modules & sections are standardized thus should NOT be changed or renumbered due to the omission of unrequired sections.

a. New applications involving generic medicinal products

For new applications of generic medicinal product , RMP modules SI to SVII may be omitted. RMP module SVIII should be based on the safety concerns of the reference medicinal product unless the generic differs significantly in properties which could relate to safety, or unless otherwise requested by the SFDA. Provided the reference medicinal product does not have any additional pharmacovigilance activities or efficacy studies imposed as a condition of the marketing authorization, RMP parts III and IV may be

omitted. Part VI should be based on an appropriately modified version of the public summary of the reference medicinal product.

Further guidance will be provided for situations where the reference medicinal product does not have a RMP.

For updates to the RMP, RMP module SV should be included.

b. New applications under Article 10c “informed consent”

For new applications, the RMP should be the same as the RMP of the cross-referred medicinal product. A RMP will still be required even if the cross-referred product does not have a RMP.

c. New applications involving hybrid or fixed combination medicinal products

Hybrid: in cases where the medicinal product does not fall within the definition of a generic medicinal product or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product.

Fixed combination: the combination of active substances within a single pharmaceutical form of administration.

For new applications of these products , only the data on the fixed combination or data relating to the differences compared with the reference medicinal product need be supplied for RMP modules SII and SIII.

d. New applications of “well established medicinal use”

When the active substance of the medicinal product have been well-established medicinal use within the concerned country for at least ten years, with recognised efficacy and an

acceptable level of safety; for new applications of these products , RMP modules SII to SIV may be omitted.

e. New applications for a product with new indications where the marketing authorisation applicant already has products with the same active substance authorised for 10 years

When an application for a new medicinal product, is for the same active substance for which the marketing authorisation applicant already has one or more existing authorised and marketed product(s) and

1. the provisions of “well established medicinal use” cannot be met; and
2. the marketing authorisation applicant does not have a risk management plan for any product containing the active substance; and
3. the currently authorised products were placed on the market in the KSA 10 or more years prior to the application.

Clinical trial data relating to the already authorised product(s) may be omitted from RMP module SIII and RMP module SIV should be written only in reference to the target population(s) of the new application unless requested otherwise by the SFDA. However, data from experience of the use of the already authorised medicinal products in the special populations which are the subject of RMP module SIV may be included.

Figure V.3. Requirements for new marketing applications

^ May be omitted under certain circumstances

* Modified requirement

f. Initial risk management plan for medicinal products on the market for 10 years

Type of new application	Part I	Part II-Module SI	Part II-Module SII	Part II-Module SIII	Part II-Module SIV	Part II-Module SV	Part II-Module SVI	Part II-Module SVII	Part II-Module SVIII	Part III	Part IV	Part V	Part VI	Part VII
New active substance	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Similar biological	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Informed consent	✓	✓	✓	✓	✓	✓	✓	✓	✓	*	*	✓	*	✓
Generic medicine	✓								✓	*	*	✓	*	✓
Hybrid medicinal products	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Fixed combination	✓	✓	^	^	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
“Well established use”	✓	✓				✓	✓	✓	✓	✓	✓	✓	✓	✓
“Same active substance”	✓	✓	*	*	*	✓	✓	✓	✓	✓	✓	✓	✓	✓

Unless otherwise requested by the SFDA, marketing authorisation holders required to submit an initial RMP for a marketed product may omit modules SIII and SIV provided the following conditions are met:

1. the product was placed on the market 10 or more years before the requirement for an RMP is established; and
2. the requirement for an RMP is not due to an application for a significant change to an existing marketing authorisation.

If condition 2 cannot be met, clinical trial data relating to this change should be supplied in RMP module SIII but RMP module SIV may be omitted. Discussion of the existing post-authorisation data and its applicability to the target population should be extensively discussed in RMP module SV.

V.C.3. Submission of the risk management plan

Currently, for authorised products, the RMP is submitted as PDF files within the eCTD/CTD submission or otherwise requested by the SFDA. Following a Commission Decision where the procedure has involved the submission of an RMP.

Marketing authorisation holders 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.

V.C.4. Updates to the risk management plan

If an RMP has previously been submitted by the applicant/marketing authorisation holder for the active substance, any following submissions shall be in the form of an update unless requested otherwise. Each submission of the RMP shall have a distinct version number and shall be dated. This applies whether the entire RMP or only a part or module is being

submitted. When technically feasible, clean and track change versions should be submitted along with a cover letter detailing the changes since the last submitted version.

There will no longer be scheduled “routine” updates to the RMP. In exceptional cases, when justified by risk, the SFDA may still specify a date for submission of the next RMP as a condition of the marketing authorisation.

It is the responsibility of the marketing authorisation holder to monitor the safety profile of the product(s) and to update and submit the RMP if there is a significant change to the risk-benefit balance

of one or more medicinal products included in the RMP. A significant change would, in particular,

usually include extension of indications, clinically important changes to the product information,

reaching an important pharmacovigilance milestone and also certain new strengths and formulations.

An updated RMP should now be submitted:

- at the request of the SFDA;
- whenever the risk management system is modified, especially as the result of new information

being received that may lead to a significant change to the risk-benefit balance or as a result of an

important pharmacovigilance or risk minimisation milestone being reached.

If, when preparing a PSUR, there is a need for consequential changes to the RMP as a result of new

safety concerns, or other data, 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, the RMP submission should be handled as a stand-alone variation.

However, in the context of a PSUR single assessment (PSUSA), as an interim measure, submission

of RMP updates cannot be accepted together with the PSURs of medicinal products. Marketing authorisation holders should take the opportunity of another upcoming procedure to update their RMP. Alternatively marketing authorisation holders should submit a separate variation to update their RMP.

For authorised medicinal products, RMP updates should be submitted to the SFDA for assessment.

When the RMP is updated, the risk minimisation plan should include an evaluation of the impact of routine and/or additional risk minimisation activities as applicable (see V.B.11.4.).

V.C.4.1. Updates to the risk management plan submitted during a procedure

A medicinal product can only have one “current” version of a RMP. If a medicinal product has more than one procedure in process at the same time which requires submission of a RMP a combined RMP should be submitted with appropriate separation of data in RMP module SIII.

If several updates to the RMP are submitted during the course of a procedure, the version considered as the “current” RMP for future updates and track changes purposes, shall be the last one submitted before the Opinion. For example, in the final weeks before the Opinion, the RMP may be updated several times to reflect the SFDA scientific committees

discussions, e.g. changed indications, changes in SPC wording which affect risk minimisation.

Following the finalisation of the procedure, the final version of the RMP should be provided in eCTD/CTD. The RMP should reflect the outcome of the procedure – ie removal of all references and data which were subject to a negative Opinion. The exception to this requirement is that populations studied in clinical trials related to a negative Opinion may be included in suitably annotated exposure data in RMP module SIII.

Unless requested otherwise, for RMPs updated during (after the start) of a procedure, track changes should show changes since the start of the procedure whilst the cover letter should show changes since the last version was submitted.

If there is an ongoing procedure for which an RMP has been submitted, “routine” updates should not be submitted during the procedure.

V.C.5. Procedure for the assessment of the risk management plan

The regulatory oversight of RMPs for authorised products lies with the Pharmacovigilance Department (and when appropriate) the pharmacovigilance committee of the national medicines authority.

The SFDA may, on a case-by-case basis, consult with healthcare professionals and patients during the assessment of RMPs to gather their input on proposed risk minimisation measures.

V.C.6. Implementation of additional risk minimisation activities

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

Marketing authorisation holders are responsible for ensuring compliance with the national conditions of the marketing authorisation for their product wherever it is used within the KSA.

The SFDA should also ensure that any conditions or restrictions with regard to the safe and effective use of authorised product are applied within the SFDA regardless of the source of the product.

ANNEX I

Risk management plans

Format of the risk management plan

The risk management plan shall consist of the following 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-authorisation experience

Module SVI: Additional EU requirements for the safety specification

Module SVII: Identified and potential risks

Module SVIII: Summary of the safety concerns

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

Part IV: Plans for post-authorisation efficacy studies

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

Part VI: Summary of the risk management plan

Part VII: Annexes

Module VI – Management And Reporting of Adverse Reactions to Medicinal Product

VI.A. Introduction

VI.A.1. Scope

This Module addresses the legal requirements by SFDA, as regards the collection, data management and reporting of suspected adverse reactions (serious and non-serious) associated with medicinal products for human use authorised in the KSA. Recommendations regarding the reporting of emerging safety issues or of suspected adverse reactions occurring in special situations are also presented in this Module. shall be applied in this Module.

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 individual case safety report or as Emerging Safety Issues. This information may however need to be collected and presented in periodic safety update reports for the interpretation of safety data or for the benefit risk evaluation of medicinal products. In this aspect, guidance provided in Module VII applies.

All applicable legal requirements detailed in this Module are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

VI.A.2. Definitions

General principles presented in the ICH-E2A and ICH-E2D guidelines¹ should be adhered to; some of these principles included as well in this chapter.

VI.A.2.1. Adverse reaction

An adverse reaction is a response to a medicinal product which is noxious and unintended.

This includes adverse reactions which arise from:

- the use of a medicinal product within the terms of the marketing authorisation;
- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- occupational exposure.

VI.A.2.1.1. 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 characterised 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.2.1.2. 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 authorised 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 authorised product information.

c. Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the authorised 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.2.2. Medicinal product

A medicinal product is characterised 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 authorised in the KSA but also to any such medicinal products commercialised outside the KSA by the same marketing authorisation holder (see VI.C.2.2). Given that a medicinal product is authorised with a defined composition, all the adverse reactions suspected to be related to any of the active substances being part of a medicinal product authorised 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, authorised 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.2.3. 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-E2D⁹

- a healthcare professional is defined as a medically-qualified person such as physician, dentist, pharmacist, nurse, coroner or as otherwise specified by local regulations;
- 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.

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.

⁹ <http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html>

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.2.4 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 hospitalisation or prolongation of existing hospitalisation, 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 jeopardise the patient or may require an intervention to prevent one of the above characteristics/consequences. Such important medical events should be considered as serious¹⁰. The EudraVigilance Expert Working Group¹¹ has co-ordinated 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 Individual Case Safety Reports (ICSRs) in the framework of the day-to-day pharmacovigilance activities.

¹⁰ Examples are provided in Section II.B of ICH E2A guideline

¹¹ <http://eudravigilance.ema.europa.eu/human/textforIME.asp>

VI.A.2.5. 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 reports

Marketing authorisation holders should take appropriate measures 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 Saudi data protection local requirement.

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 marketing authorisation holders 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-authorisation 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, marketing authorisation holder 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 organised data collection systems where adverse events reporting is actively sought, as defined in VI.B.1.2.

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’ organisations to their members, or class action lawsuits should be considered spontaneous reports.

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 risk-benefit balance of medicinal products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorisation holders 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 marketing

authorisation holder 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 properties¹². In addition, marketing authorisation holders should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, 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 marketing authorisation holders to identify and record ICSRs originating from spontaneous reports or non-interventional post-authorisation studies.

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 marketing authorisation holder(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 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 marketing authorisation holders.

VI.B.1.1.3. Reports from other sources

If a marketing authorisation holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it should be handled as a spontaneous report. Every attempt should be made to follow-up

¹² See VI. Appendix 2. for the detailed guidance on the monitoring of medical and scientific literature.

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

Marketing authorisation holders should regularly screen internet or digital media¹³ 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 marketing authorisation holder¹⁴. 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. Marketing authorisation holders may also consider utilising their websites to facilitate the collection of reports of suspected adverse reactions.

If a marketing authorisation holder 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 reporting.

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

¹³ Although not exhaustive, the following list should be considered as digital media: web site, web page, blog, vlog, social network, internet forum, chat room, health portal.

¹⁴ A donation (financial or otherwise) to an organisation/site by a marketing authorisation holder does not constitute ownership, provided that the marketing authorisation holder does not control the final content of the site.

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 organised data collection systems, which include clinical trials, non-interventional studies, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers, compassionate use or named 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 certain compassionate use or named patient use where adverse events are not actively sought.

For the purpose of safety reporting, 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 the criteria for reporting.

General reporting rules for suspected adverse reactions occurring in organised data collection systems conducted in the KSA.

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). This is:

- One or more identifiable reporter (primary source), characterised by qualification (e.g. physician, pharmacist, other healthcare professional, consumer or other non-healthcare

professional) name, initials or address¹⁵. 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 organisation 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 characterised by initials, patient identification number, date of birth, age, age group or gender. The information should be as complete as possible¹⁶.
- One or more suspected substance/medicinal product (see VI.A.2.2).
- One or more suspected adverse reaction (see VI.A.2.1). 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 marketing authorisation holder) agrees with this, the report does not qualify as a valid ICSR since the minimum information is incomplete¹⁷. 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 marketing authorisation holder is made aware that a

¹⁵ Local data privacy laws regarding patient's and reporter's identifiability might apply

¹⁶ See Footnote 4.

¹⁷ There is no suspected adverse reaction

patient was hospitalised 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 reporting. Marketing authorisation holders 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 marketing authorisation holder 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 ICSR¹⁸.

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.2.1.1). In this situation, the opinions of both the consumer and the healthcare professional should be included in the ICSR. Guidance on the reporting

¹⁸ 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) guideline.

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.3. 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). Any attempt to obtain follow-up information should be documented.

Follow-up methods should be tailored towards optimising 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 ICSR¹⁹.

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. A business process map in relation to the mandatory follow-up of information for the identification of suspected biological medicinal products is presented in VI.Appendix 1..

For cases related to vaccines, the recommendations provided in the Guideline on the conduct of Pharmacovigilance for Vaccines for Pre-and Post-exposure Prophylaxis against Infectious Diseases should also be followed as appropriate. See annex 3.

VI.B.4. 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. With regards to patient's and reporter's identifiability, case report information should be transmitted between

¹⁹ For further guidance on reporting this information, refer to ICH-E2B(R2) guideline, Section A.1.14 ("Was the case medically confirmed, if not initially from a healthcare professional?").

stakeholders (marketing authorisation holders 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 authorised 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 organisation or between organisations 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.5. Quality management

Marketing authorisation holders 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.6. Special situations

VI.B.6.1. Use of a medicinal product during pregnancy or breastfeeding

a. Pregnancy

Reports, where the embryo or foetus 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. The recommendations provided in the Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data²⁰ should be considered as regard the monitoring, collection and reporting of information in these specific situations in order to facilitate the scientific evaluation. When an active substance (or one of its metabolites) has a long half-life, this should be taken into account 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 marketing authorisation holders 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 foetus 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.

²⁰ (Ref.: EMEA/CHMP/313666/2005)

This especially refers to:

- reports of congenital anomalies or developmental delay, in the foetus or the child;
- reports of foetal 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 periodic safety update reports (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 authorisation or stipulated in the risk management plan; 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.7²¹

VI.B.6.2. Use of a medicinal product in a paediatric or elderly population

The collection of safety information in the paediatric 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.

As regards the paediatric population, the guidance published by the Agency²² on the conduct of pharmacovigilance in this population should be followed.

VI.B.6.3. 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 periodic safety update reports as applicable. When those reports constitute safety issues impacting on the risk-benefit balance of the medicinal product, they should be notified to the SFDA in accordance with the recommendations provided in VI.C.2.1.6.

²¹ 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/>

²² Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (EMA/CHMP/PhVWP/235910/2005- rev.1).

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, unauthorised indication or population, etc.).

VI.B.6.4. Lack of therapeutic efficacy

Reports of lack of therapeutic efficacy should be recorded and followed-up if incomplete. They should not normally be reported, but should be discussed in periodic safety update reports as applicable. However, in certain circumstances, reports of lack of therapeutic efficacy may require to be reported within a 15-day time frame (See VI.C.6.2.3.4 as regards electronic reporting in the KSA). Medicinal products used in critical conditions or for the treatment of life-threatening diseases, vaccines, contraceptives are examples of such cases. 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 vaccinees, 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-authorisation safety studies as appropriate. General

guidance regarding the monitoring of vaccines failure, provided in the Report of CIOMS/WHO Working Group on Vaccine Pharmacovigilance²³, may be followed.

VI.B.7. 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 marketing authorisation holder, 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 marketing authorisation holder has set up contractual arrangements with a person or an organisation, explicit procedures and detailed agreements should exist between the marketing authorisation holder and the person/organisation to ensure that the marketing authorisation holder 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/organisation to perform literature searches and/or report valid ICSRs, detailed agreements should exist to ensure that the marketing authorisation holder 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

²³[Definition and Application of Terms for vaccine Pharmacovigilance, 2012](#)

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.7.1. Reporting time frames

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 centre of the SFDA or by any personnel of the marketing authorisation holder, 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.8. Reporting modalities

Taking into account the international dimension of adverse reactions reporting and the need to achieve harmonisation 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, marketing authorisation holders should adhere to the following internationally agreed ICH²⁴ guidelines and standards:

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

²⁴ <http://www.ich.org/>

- 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 taken into account.

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 authorised in the KSA.

VI.C.1. Interface with safety reporting rules for clinical trials and post authorisation studies in the KSA

Post-authorisation safety or efficacy studies requested by the SFDA, or conducted voluntarily by marketing authorisation holders, can either be clinical trials or non-interventional studies as shown in Figure VI.1.

Further guidance on post-authorisation 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 National Pharmacovigilance and drug Safety Center (NPC) database

Section D: Post-authorisation safety or efficacy clinical trials requested by SFDA or conducted voluntarily by marketing authorisation holders, due to the nature of the intervention.

Section E: Non-interventional post-authorisation safety or efficacy studies requested or conducted voluntarily by the marketing authorisation holders and which follow the same legal requirements.

Section F: Non-interventional post-authorisation studies conducted in accordance with SPC indication and condition of use.

VI.C.1.1. Interface with 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-authorisation safety or efficacy study, or conducted voluntarily.

If a clinical trial, yields safety concerns which impact on the risk-benefit balance of an authorised medicinal product, the SFDA where the medicinal product is authorised 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 periodic safety update report of the authorised medicinal product are detailed in Module VII.

VI.C.1.2. Interface with post-authorisation studies

post-authorisation studies include non-interventional post-authorisation studies, compassionate use, named patient use, other patient support and disease management programmes, 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 marketing authorisation holders 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 standardised 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 marketing authorisation holders.

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-authorisation 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 marketing authorisation holder of the suspected medicinal product, but not to both to avoid duplicate and while respecting the electronic reporting recommendations detailed in V.I.C.6.2.1.7.

Further guidance on post-authorisation studies conducted by marketing authorisation holders 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 marketing authorisation holder, the marketing authorisation holder 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 organised 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 summarised 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 summarised 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 organisation 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 reports

VI.C.2.1. Marketing authorisation holders responsibilities

Each marketing authorisation holder 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-authorisation study.

Marketing authorisation holders 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 authorised medicinal products shall be retained as long as the product is authorised and for at least 10 years after the marketing authorisation 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, marketing authorisation holders responsibilities apply to reports related to medicinal products (see VI.A.2.2) 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 marketing authorisation holder shall ensure that any information on adverse reactions, suspected to be related to at least one of the active substances of its medicinal products

authorised 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 marketing authorisation holder when having concluded a commercial agreement with a company outside the KSA for one of its medicinal product authorised in the KSA. The clock for reporting starts 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 marketing authorisation holders to all reports of suspected adverse reactions.

VI.C.2.1.1. Spontaneous reports

Marketing authorisation holders 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. In this context, marketing authorisation holders may consider utilising their websites 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

Marketing authorisation holders shall record all reports of suspected adverse reactions originating from or outside the KSA, which occur in post-authorisation studies, initiated, managed, or financed by them. General guidance on post-authorisation studies is provided in VI.C.1.2. Electronic reporting recommendations for cases originating in post-authorisation studies are detailed in VI.C.6.2.2.7.

For post authorisation studies, marketing authorisation holders 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. Marketing authorisation holders 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 marketing authorisation holder 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 periodic safety update report of the authorised 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 periodic safety update reports (see Module VII).

Marketing authorisation holders should monitor all the active substances for which they hold a marketing authorisation 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 marketing authorisation holder 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 marketing authorisation holder can be excluded on the basis of the criteria detailed in VI.C.2.1.;
- For individual case safety reports identified in the scientific and medical literature that originate in a country where a company holds a marketing authorisation but has never commercialised the medicinal product;
- For literature articles, which present data analyses from publicly available databases or, which summarise results from post-authorisation 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 risk-benefit 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 periodic safety update report (see Module VII) and analysed as regards their overall impact on the medicinal product risk-benefit profile. In addition, any new safety information, which may impact on the risk-benefit profile of a medicinal product, should be notified immediately to the SFDA in accordance with the recommendations provided in VI.C.2.1.6. A detailed guidance on the monitoring of the scientific and medical literature has been developed; it is included in VI. Appendix 2. 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, marketing authorisation holders 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, haemovigilance procedures may also apply. Therefore the marketing authorisation holder 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 risk-benefit 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-authorisation 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 risk-benefit balance of the medicinal product and/or have implications for public health;
- safety issues related to the use outside the terms of the marketing authorisation;

- safety issues due to misinformation in the product information;
- marketing authorisation 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;
- lack of supply of medicines.

These events/observations, which may affect the risk-benefit balance of a medicinal product, are not to be submitted as ICSRs. They should be notified as Emerging Safety Issues in writing to the SFDA where the medicinal product is authorised and to the SFDA via email (NPC.Drug@sfda.gov.sa); this should be done immediately when becoming aware of them. The document should indicate the points of concern and the actions proposed in relation to the marketing application/authorisation for the concerned medicinal product. Those safety issues should also be analysed in the relevant sections of the periodic safety update report of the authorised medicinal product.

VI.C.2.1.7. Period between the submission of the marketing authorisation application and the granting of the marketing authorisation

In the period between the submission of the marketing authorisation application and the granting of the marketing authorisation, information (quality, non-clinical, clinical) that could impact on the risk-benefit 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 authorisation

The marketing authorisation holder shall continue to collect any reports of suspected adverse reactions related to the concerned medicinal product following the suspension of a marketing authorisation. The reporting requirements outlined in VI.C.4 remain.

Where a marketing authorisation is withdrawn or revoked, the former marketing authorisation holder 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 programmes and market research programmes

A patient support programme is an organised system where a marketing authorisation holder receives and collects information relating to the use of its medicinal products. Examples are post-authorisation patient support and disease management programmes, surveys of patients and healthcare providers, information gathering on patient compliance, or compensation/re-imburement schemes.

A market research programme refers to the systematic collection, recording and analysis by a marketing authorisation holder of data and findings about its medicinal products, relevant for marketing and business development.

Safety reports originating from those programmes should be considered as solicited reports. Marketing authorisation holders 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

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.

- serious valid ICSRs shall be reported by marketing authorisation holders within 15 days from the date of receipt of the reports;
- non-serious valid ICSRs shall be reported by marketing authorisation holders within 90 days from the date of receipt of the reports.

This should be done in accordance with the reporting modalities detailed in VI.C.4.

a. Serious ICSRs

- Marketing authorisation holders shall report all serious ICSRs that occur in the KSA.
- Marketing authorisation holders shall report to the NPC database all serious ICSRs that occur outside the KSA.

b. Non-Serious ICSRs

- If required by the SFDA, marketing authorisation holders 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.C.6.2.1.4). 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 V²⁵.

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

²⁵ Council for International Organizations of Medical Sciences (CIOMS). Current Challenges in Pharmacovigilance: Pragmatic Approaches (CIOMS V). Geneva: CIOMS; 2001. <http://www.cioms.ch/>.

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 ICH E2B(R2) data element A.1.4 'Type of report' should be populated with the value 'Spontaneous'.
- 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 15 or 90-day time frame,
- 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.

VI. Appendix 1: Identification of biological medicinal products

Figure VI.2. Business process map - Identification of biological medicinal products

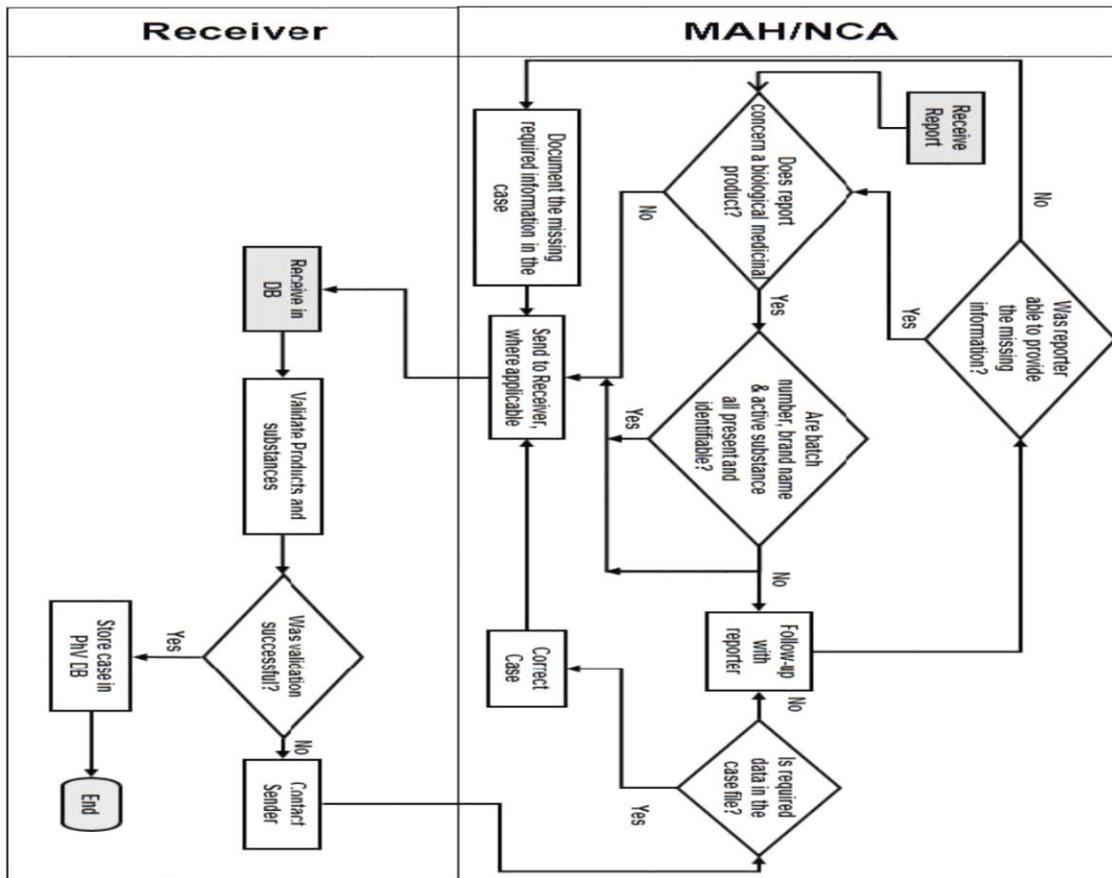


Table VI.1. Process description- Identification of biological medicinal product

No.	Step	Description	Responsible Organisation
1	Start. Receive report.	Day 0. Receipt of the information for the case that indicates that one of the suspect drugs is of biological origin.	MAH/NCA
2	Does report concern a biological medicinal product?	If Yes, go to step 3 If No, go to step 4	
3	Are batch number, brand name & active substance all present and identifiable?	If Yes, create the case and send it to the correct receiver (step 3). If there is more than one batch number, structure the batch number that coincided with the adverse reaction in the Drug section (ICH-E2B(R2) B.4) and enter the other batch numbers in the case narrative. If No, create the case and send it to the correct receiver (step 3) and follow-up with the reporter (step 3.1).	MAH/NCA
3.1	Follow-up with reporter.	Follow-up with the reporter to attempt to identify the missing information.	MAH/NCA
3.2	Was reporter able to provide the missing information?	If Yes, return to step 1 – the information should be treated as follow-up and a new version created & transmitted.	MAH/NCA

No.	Step	Description	Responsible Organisation
		If No, document this (step 3.3).	
3.3	Document the required missing information in the case.	Document in the case that the missing required information has been sought but the reporter was not able or willing to provide it.	MAH/NCA
4	Send to receiver, where applicable.	If the case requires transmission to a receiver, transmit the case [if applicable electronically, in E2B(R2) format] within the relevant timelines (15 or 90 days), to the relevant receiver.	MAH/NCA
5	Receive in DataBase (DB).	Receive the case electronically and load it into the pharmacovigilance database.	Receiver
6	Validate products and substances	Validate the products and substances to ensure that the brand name, active substance & batch number are all present and identifiable. This validation should be complementary to the usual business rules validations.	Receiver

No.	Step	Description	Responsible Organisation
7	Was validation successful?	If Yes, store the case in the pharmacovigilance database (step 8). If No, contact the sender (Step 7.1).	Receiver
7.1	Contact sender.	Contact the sender regarding the missing or not identifiable information.	Receiver
7.2	Is required data in the case file?	Upon receipt of communication from the receiver, check in the case file to see if the missing or unidentifiable information is already on file. If it is on file, correct the case (step 7.3). If the information is not on file, contact the reporter to request the missing information (step 3.1).	MAH/NCA
7.3	Correct case.	Correct the case to include the missing information & send updated version to receiver (step 4).	MAH/NCA
8	Store case in Pharmacovigilance DataBase (PhV DB).	The case should now be stored in the pharmacovigilance database.	Receiver
9	End.	The case is now available for signal detection and data quality analyses.	

VI. Appendix 2 Detailed guidance on the monitoring of scientific and medical literature

VI. App1.1 When to start and stop searching in the scientific and medical literature

KSA specific requirements, as regards the monitoring of scientific and medical literature are provided in VI.C.2.1.3.

In addition to the reporting of serious and non-serious ICSRs or their presentation in periodic safety update reports, the marketing authorisation holder has an obligation to review the worldwide experience with medicinal product in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation. The worldwide experience includes published scientific and medical literature. For the period between submission and granting of a marketing authorisation, literature searching should be conducted to identify published articles that provide information that could impact on the risk-benefit assessment of the product under evaluation. For the purpose of the preparation of periodic safety update reports (See Module VII) and the notification of Emerging Safety Issues (See VI.C.2.1.6), the requirement for literature searching is not dependent on a product being marketed. Literature searches should be conducted for all products with a marketing authorisation, irrespective of commercial status. It would therefore be expected that literature searching would start on submission of a marketing authorisation application and continue while the authorisation is active.

VI. App1.2 Where to look

Articles relevant to the safety of medicinal products are usually published in well-recognised scientific and medical journals, however, new and important information may be first presented at international symposia or in local journals. Although the most well-known databases (e.g. Medline) cover the majority of scientific and medical journals, the

most relevant publications may be collated elsewhere in very specialised medical fields, for certain types of product (e.g. herbal medicinal products) or where safety concerns are subject to non-clinical research. A marketing authorisation holder should establish the most relevant source of published literature for each product.

Medline, Embase and Excerpta Medica are often used for the purpose of identifying ICSRs. These databases have broad medical subject coverage. Other recognised appropriate systems may be used. The database providers can advise on the sources of records, the currency of the data, and the nature of database inclusions. It is best practice to have selected one or more databases appropriate to a specific product. For example, in risk-benefit assessment, safety issues arising during non-clinical safety studies may necessitate regular review of a database that has a less clinical focus and includes more laboratory-based publications.

Relevant published abstracts from meetings and draft manuscripts should be reviewed for reportable ICSRs and for inclusion in periodic safety update reports. Although it is not a requirement for marketing authorisation holders to attend all such meetings, if there are company personnel at such a meeting, or it is sponsored by a marketing authorisation holder, it is expected that articles of relevance would be available to the marketing authorisation holder's pharmacovigilance system. In addition, literature that is produced or sponsored by a marketing authorisation holder should be reviewed, so that any reportable ICSRs can be reported as required in advance of publication.

If ICSRs are brought to the attention of a marketing authorisation holder from this source, they should be processed in the same way as ICSRs found on searching a database or reviewing a journal. Abstracts from major scientific meetings are indexed and available in some databases, but posters and communications are rarely available from this source.

VI. App1.3 Database Searches

A search is more than a collection of terms used to interrogate a database. Decisions about the database selection, approach to records retrieval, term or text selection and the

application of limits need to be relevant to the purpose of the search. For searches in pharmacovigilance, some of the considerations for database searching are described below.

VI. App1.3.1 Precision and recall

Medical and scientific databases are a collection of records relating to a set of publications. For any given record, each database has a structure that facilitates the organisation of records and searching by various means, from simple text to complex indexing terms with associated subheadings. Search terms (text or indexed) can be linked using Boolean operators and proximity codes to combine concepts, increasing or decreasing the specificity of a search. In addition, limits to the output can be set. When searching, the application of search terms means that the output is less than the entire database of the records held. The success of a search can be measured according to precision and recall (also called sensitivity). Recall is the proportion of records retrieved ("hits") when considering the total number of relevant records that are present in the database. Precision is the proportion of "hits" that are relevant when considering the number of records that were retrieved. In general, the higher recall searches would result in low precision.

VI. App1.3.2 Search construction

Databases vary in structure, lag time in indexing and indexing policy for new terms. While some database providers give information about the history of a particular indexing term or the application of synonyms, other databases are less sophisticated. In addition, author abstracts are not always consistent in the choice of words relating to pharmacovigilance concepts or medicinal products/active substances names.

When constructing a search for pharmacovigilance, the highest recall for a search would be to enter the medicinal product name and active substance name (in all their variants) only. In practice, additional indexing terms and text are added to increase precision and to reduce the search result to return records that are of relevance to pharmacovigilance. There is a balance to be achieved. It is, therefore, expected that complicated searches are

accompanied by initial testing to check that relevant records are not omitted, however, there is no defined acceptable loss of recall when searching for pharmacovigilance purposes. Term selection should be relevant to the database used and the subject of the search.

VI. App1.3.3 Selection of product terms

Searches should be performed to find records for active substances and not for brand names only. This can also include excipients or adjuvants that may have a pharmacological effect. When choosing search terms for medicinal products, there are a number of considerations.

- Is the active substance an indexed term?
- What spellings might be used by authors (particularly if the active substance is not indexed)?
- What alternative names might apply (numbers or codes used for products newly developed, chemical names, brand names, active metabolites)?
- Is it medically relevant to search only for a particular salt or specific compound for an active substance?

During searches for ICSRs, it may be possible to construct a search that excludes records for pharmaceutical forms or routes of administration different to that of the subject product, however, restrictions should allow for the inclusion of articles where this is not specified. Search construction should also allow for the retrieval of overdose, medication error, abuse, misuse, off-label use or occupational exposure information, which could be poorly indexed. Searches should also not routinely exclude records of unbranded products or records for other company brands.

VI. App1.3.4 Selection of search terms

As described previously, there is no acceptable loss of recall when searching published literature for pharmacovigilance. The use of search terms (free text or use of indexing) to

construct more precise searches may assist in managing the output. Deficiencies that have been found frequently during the SFDA inspections include:

- the omission of outcome terms, for example "death" as an outcome may be the only indexed term in a case of sudden death;
- the omission of pregnancy terms to find adverse outcomes in pregnancy for ICSR reporting;
- the omission of terms to include special types of reports which needs to be addressed as well in periodic safety update reports, for example,
 - Reports of asymptomatic overdose, medication error, off-label use, misuse, abuse, occupational exposure;
 - Reports of uneventful pregnancy.

VI. App1.3.5 Limits to a search

Some databases apply indexing that allows the application of limits to a search, for example by subject age, sex, publication type. The limits applied to a search are not always shown in the "search strategy" or search string.

If limits are applied, they should be relevant to the purpose of the search. When searching a worldwide scientific and medical literature database, titles and abstracts are usually in English language. The use of limits that reduce the search result to only those published in the English language is generally not acceptable. Limits applied to patient types, or other aspects of an article, for example human, would need to be justified in the context of the purpose of a search.

Limits can be applied to produce results for date ranges, for example, weekly searches can be obtained by specifying the start and end date for the records to be retrieved. Care should be taken to ensure that the search is inclusive for an entire time period, for example, records that may have been added later in the day for the day of the search should be covered in

the next search period. The search should also retrieve all records added in that period, and not just those initially entered or published during the specified period (so that records that have been updated or retrospectively added are retrieved). This should be checked with the database provider if it is not clear.

Although one of the purposes of searching is to identify ICSRs for reporting, the use of publication type limits is not robust. ICSRs may be presented within review or study publications, and such records may not be indexed as "case-reports", resulting in their omission for preparation of periodic safety update reports from search results limited by publication type.

VI. App1.4 Record keeping

Records of literature searches should be maintained in accordance with the requirements described in [IR Art 12]. Marketing authorisation holders should demonstrate due diligence in searching published scientific and medical literature. It is always good practice to retain a record of the search construction, the database used and the date the search was run. In addition, it may be useful to retain results of the search for an appropriate period of time, particularly in the event of zero results. If decision making is documented on the results, it is particularly important to retain this information.

VI. App1.5 Outputs

Databases can show search results in different ways, for example, titles only or title and abstract with or without indexing terms. Some publications are of obvious relevance at first glance, whereas others may be more difficult to identify. Consistent with the requirement to provide the full citation for an article and to identify relevant publications, the title, citation and abstract (if available) should always be retrieved and reviewed.

VI. App1.6 Review and selection of articles

It is recognised that literature search results are a surrogate for the actual article. Therefore, it is expected that the person reviewing the results of a search is trained to identify the

articles of relevance. This may be an information professional trained in pharmacovigilance or a pharmacovigilance professional with knowledge of the database used. Recorded confirmation that the search results have been reviewed will assist in demonstrating that there is a systematic approach to collecting information about suspected adverse reactions from literature sources. It is recommended that quality control checks are performed on a sample of literature reviews / selection of articles to check the primary reviewer is identifying the relevant articles.

A common issue in selecting relevant articles from the results of a search is that often this process is conducted for the purposes of identification of ICSRs only. Whereas the review should also be used as the basis for collating articles for the periodic safety update report production, therefore relevant studies with no ICSRs should also be identified, as well as those reports of events that do not qualify for reporting.

Outputs from searches may contain enough information to be a valid ICSR, in which case the article should be ordered. All articles for search results that are likely to be relevant to pharmacovigilance requirements should be obtained, as they may contain valid ICSRs or relevant safety information. The urgency with which this occurs should be proportionate to the content of the material reviewed and the resulting requirement for action as applicable for the marketing authorisation holder.

Articles can be excluded from reporting by the marketing authorisation holder 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. Alternative reasons for the exclusion of a published article for the reporting of ICSRs are detailed in VI.C.2.1.3.

VI. App1.7 Day zero

As described in VI.B.7, day zero is the date on which an organisation becomes aware of a publication containing the minimum information for an ICSR to be reportable. Awareness of a publication includes any personnel of that organisation, or third parties with

contractual arrangements with the organisation. It is sometimes possible to identify the date on which a record was available on a database, although with weekly literature searching, day zero for a reportable adverse reaction present in an abstract is taken to be the date on which the search was conducted. For articles that have been ordered as a result of literature search results, day zero is the date when the minimum information for an ICSR to be valid is available. Organisations should take appropriate measures to obtain articles promptly in order to confirm the validity of a case.

VI. App1.8 Duplicates

Consistent with the requirements for reporting ICSRs, literature cases should be checked to prevent reporting of duplicates, and previously reported cases should be identified as such when reported. It is, therefore, expected that ICSRs are checked in the organisation database to identify literature articles that have already been reported.

VI. App1.9 Contracting out Literature Search Services

It is possible to use the services of another party to conduct searches of the published scientific and medical literature. In this event, the responsibility for the performance of the search and subsequent reporting still remains. The transfer of a pharmacovigilance task or function should be detailed in a contract between the organisation and the service provider. The nature of third party arrangements for literature searching can range from access to a particular database interface only (access to a technology) to full literature searching, review and reporting (using the professional pharmacovigilance services of another organisation). It is recognised that more than one organisation may share services of a third party to conduct searches for generic active substances. In this instance, each organisation should satisfy itself that the search and service is appropriate to their needs and obligations. Where an organisation is dependent on a particular service provider for literature searching, it is expected that an assessment of the service(s) is undertaken to determine whether it

meets the needs and obligations of the organisation. In any case, the arrangement should be clearly documented.

The clock start for the reporting of ICSRs begins with awareness of the minimum information by either the organisation or the contractual partner (whichever is the earliest). This also applies where a third party provides a review or a collated report from the published scientific and medical literature, in order to ensure that published literature cases are reported as required within the correct time frames. That is, day zero is the date the search was run if the minimum criteria are available in the abstract and not the date the information was supplied to the organisation.

VI. App1.10 Electronic submission of copies of articles published in the scientific and medical literature

Until standards for the electronic transmission of attachments (e.g. copies of literature articles) are developed in the framework of ICH, the sender should follow the rules outlined below for the submission of a copy of the literature article:

1. Mailing address and format of literature articles: Literature articles reportable to the SFDA should be provided in PDF format and sent via e-mail to the following e-mail address NPC.Drug@sfda.gov.sa.

In relation to copies of articles from the published scientific and medical literature, marketing authorisation holders are recommended to consider potential copyright issues specifically as regards the electronic transmission and handling of electronic copies in the frame of regulatory activities.

2. File name of literature articles sent in electronic format to the SFDA:

The file name of a literature article sent in PDF format should match exactly the ‘World-Wide Unique Case Identification Number’ (ICH-E2B(R2) A.1.10.1 or A.1.10.2 as applicable) assigned to the individual case, which is described in the article and which is reported in the E2B(R2) ICSR format.

If there is a follow-up article to the individual case published in the literature, the file name with the World-Wide Unique Case Identification Number must be maintained but should include a sequence number separated with a dash.

Examples:

- Initial ICSR published in the literature: FR-ORGABC-23232321 (data element ‘World-Wide Unique Case Identification Number’ (ICH-E2B(R2) A.1.10.1));
 - File name of the literature article: FR-ORGABC-23232321.pdf.
- Follow-up information published in the literature in a separate article:
 - ICSR: FR-ORGABC-23232321 (data element World-Wide Unique Case Identification Number remains unchanged (ICH-E2B(R2) A.1.10.1));
 - File name: FR-ORGABC-23232321-1.pdf.

3. Reporting of cases reported in the scientific and medical literature referring to more than one patient:

When the literature article refers to the description of more than one patient, the copy of the literature article should be sent only once.

The file name of a literature article sent in PDF format should match exactly the ‘World-Wide Unique Case Identification Number’ (data element ICH-E2B(R2) A.1.10.1 or A.1.10.2 as applicable) assigned to the first reportable individual case described in the article.

In addition, all ICSRs which relate to the same literature article should be cross referenced in the data element ‘Identification number of the report which is linked to this report’ (ICH-E2B(R2) A.1.12). The data element should be repeated as necessary to cross refer all related cases (see Table VI.2).

Table VI.2. Examples for the reporting of ICSRs described in the scientific and medical literature and referring to more than one patient

Ex	Scenario	Action
1	<p>A literature article describes suspected adverse reactions that have been experienced by up to 3 single patients.</p> <p>3 ICSRs should be created and reported for each individual identifiable patient described in the literature article.</p> <p>Each ICSR should contain all the available information on the case.</p>	<p>For Case 1 described in the literature article:</p> <p>ICH-E2B(R2) A.1.10.1 ‘World-Wide Unique Case Identification Number’: UK-ORGABC-0001</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of the report which is linked to this report’: UK-ORGABC-0002</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of the report which is linked to this report’: UK-ORGABC-0003</p> <p>ICH-E2B(R2) A.2.2 ‘Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15.</p> <p>File name for the copy of literature article to be sent via e-mail: UK-ORGABC-0001.pdf</p> <p>For Case 2 described in the literature article:</p> <p>ICH-E2B(R2) A.1.10.1 ‘World-Wide Unique Case Identification Number’: UK-ORGABC-0002</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of</p>

Ex	Scenario	Action
		<p>the report which is linked to this report': UK-ORGABC-0001</p> <p>ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0003</p> <p>ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15.</p> <p>No copy of the literature article required since the copy was already submitted for case 1.</p> <p>For Case 3 described in the literature article:</p> <p>ICH-E2B(R2) A.1.10.1 'World-Wide Unique Case Identification Number': UK-ORGABC-0003</p> <p>ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0001</p> <p>ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report': UK-ORGABC-0002</p> <p>ICH-E2B(R2) A.2.2 'Literature reference(s): Literature reference in line with uniform</p>

Ex	Scenario	Action
		<p>requirements for manuscripts submitted to biomedical journals: N Engl J Med. 1997;336:309-15.</p> <p>No copy of the literature article required since the copy was already submitted for case 1.</p>
2	<p>A literature article describes suspected adverse reactions that have been experienced by more than 3 single patients.</p> <p>ICSRs should be created and reported for each individual identifiable patient described in the literature article.</p> <p>Each ICSR should contain all the available information on the case.</p> <p>The cross reference with all the linked ICSRs from this literature article should only be provided in the first case, in the data element ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report'. There is no need to</p>	<p>For the ICSRs which relate to the same literature article, the cross reference in the data element 'Identification number of the report which is linked to this report' ICH (E2B(R2) field A.1.12) should be conducted as follows:</p> <p>The first case should be linked to all other cases related to the same article;</p> <p>All the other cases should be only linked to the first one, as in the example below.</p> <p><i>Example for the reporting of cases originally reported in the scientific and medical literature referring to a large number of patients:</i></p> <p>For Case 1 described in the literature article:</p> <p>ICH E2B(R2) A.1.10.1 'Worldwide Unique Case Identification Number': UK-ORGABC-0001</p> <p>ICH-E2B(R2) A.1.12 'Identification number of the report which is linked to this report':</p>

Ex	Scenario	Action
	<p>repeat all the cross references in the other ICSRs.</p>	<p>UK-ORGABC-0002</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of the report which is linked to this report’: UK-ORGABC-0003</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of the report which is linked to this report’: UK-ORGABC-0004</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of the report which is linked to this report’: UK-ORGABC-000N</p> <p>ICH-E2B(R2) A.2.2 ‘Literature reference(s)’: N Engl J Med. 1997;336:309-15.</p> <p>File name for the copy of literature article to be sent via e-mail: UK-ORGABC-0001.pdf.</p> <p>For Case 2 described in the literature article:</p> <p>ICH E2B(R2) A.1.10.1 ‘Worldwide Unique Case Identification Number’: UK-ORGABC-0002</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of the report which is linked to this report’: UK-ORGABC-0001</p> <p>ICH-E2B(R2) A.2.2 ‘Literature reference(s)’: N Engl J Med. 1997;336:309-15.</p>

Ex	Scenario	Action
		<p>No copy of the literature article required since the copy was already submitted for case 1.</p> <p>For Case N described in the literature article:</p> <p>ICH-E2B(R2) A.1.10.1 ‘Worldwide Unique Case Identification Number’: UK-ORGABC-000N</p> <p>ICH-E2B(R2) A.1.12 ‘Identification number of the report which is linked to this report’: UK-ORGABC-0001</p> <p>ICH-E2B(R2) A.2.2 ‘Literature reference(s)’: N Engl J Med. 1997;336:309-15.</p> <p>No copy of the literature article required since the copy was already submitted for case 1</p>

VI. Appendix 2 Nullification of cases

General principles regarding the nullification of cases are provided in VI.C.6.2.2.10. The following recommendations should also be applied:

- The value in the data element ‘Report nullification’ (ICH-E2B(R2) A.1.13) should be set to ‘Yes’ and the nullification reason should be provided in the data element ‘Reason for nullification’ (ICH-EB(R2) A.1.13.1). The nullification reason should be clear and concise to explain why this case is no longer considered to be a valid report. For example a nullification reason stating, ‘the report no longer meets the reporting criteria’ or ‘report sent previously in error’ are not detailed enough explanations.
- An individual case can only be nullified by the sending organisation.

- Once an individual case has been nullified, the case cannot be reactivated.
- If it becomes necessary to resubmit the case that has been previously nullified, a new ‘Sender’s (case) safety report unique identifier’ (ICH-E2B(R2) A.1.0.1) and ‘Worldwide unique case identification number’ (ICH-E2B(R2) A.1.10) should be assigned.
- Individual versions (i.e. follow-up reports) of a case cannot be nullified, only the entire individual case to which they refer.

Table VI.3. Examples of scenarios for which ICSRs should be nullified

Ex.	Scenario	Action
1	An individual case has been identified as a duplicate of another individual case previously submitted.	One of the individual cases should be nullified. The remaining valid case should be updated with any additional relevant information from the nullified case.
2	A wrong ‘Worldwide unique case identification number’ (ICH-E2B(R2) A.1.10) was accidentally used and does not refer to an existing case.	The case with the wrong ‘Worldwide unique case identification number’ (ICH-E2B(R2) A.1.10) should be nullified. A new case should be created with a correct ‘Worldwide unique case identification number’.
3	On receipt of further information it is confirmed that the adverse reaction occurred before the suspect drug(s) was taken.	The case should be nullified.

Ex.	Scenario	Action
4	On receipt of further information on an individual case, it is confirmed that the patient did not receive the suspect drug. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	The case should be nullified.
5	On receipt of further information it is confirmed by the same reporter that the reported adverse reaction(s) did not occur to the patient. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	The case should be nullified.
6	On receipt of further information it is confirmed that there was no valid patient for the individual case. Minimum reporting criteria for an ICSR as outlined in VI.B.2 are no longer met.	If it is not possible to obtain confirmation of the patient's existence, then the case should be nullified.

□ □ Individual cases that have been nullified should not be used for scientific evaluation, however, they should remain in the database for auditing purposes.

- In addition, in case of duplicate reports where one report needs to be nullified, the update of the remaining case should be performed in the form of a follow-up report⁴⁶. Information on the identification of the nullified case(s) should be provided in the data element

‘Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)’ (ICH-E2B(R2) A.1.11.1) and in the data element ‘Case identifier(s)’ (ICH-E2B(R2) A.1.11.2).

Table VI.4. Examples of scenarios for which ICSRs should **NOT** be nullified

Ex.	Scenario	Action
7	A wrong ‘Worldwide unique case identification number’ (ICH E2B(R2) A.1.10) was accidentally used. This wrong ICH-E2B(R2) A.1.10 ‘Worldwide unique case identification number’ referred to an existing case.	<p>The report with the wrong ‘Worldwide unique case identification number’ (ICH-E2B(R2) A.1.10) should not be nullified.</p> <p>A follow-up report should be submitted to correct the information previously submitted.</p> <p>A new ICSR should be created and submitted with the correct ‘Worldwide unique case identification number’.</p>
8	On receipt of further information on an individual case, it is confirmed that the patient did not receive the marketing authorisation holder’s suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for an ICSR are still met.	The case should not be nullified.

Ex.	Scenario	Action
9	On receipt of further information the reporter has confirmed that the reported adverse reaction is no longer considered to be related to the suspect medicinal product(s).	<p>The case should not be nullified.</p> <p>A follow-up report should be submitted within the appropriate time frame with the updated information on the case.</p>
10	Change of the individual case from serious to non-serious (downgrading).	<p>The case should not be nullified.</p> <p>A follow-up report should be submitted with the data element ‘Seriousness’ (ICH-E2B(R2) A.1.5.1) populated with the value ‘No’ without selection of a value for the data element ‘Seriousness criteria’ (ICH-E2B(R2) A.1.5.2).</p> <p>The data element ‘Does this case fulfil the local criteria for an expedited report?’ (ICH-E2B(R2) field A.1.9) should remain populated with the value ‘Yes’.</p>
11	The primary source country has changed, which has an impact on the ICH-E2B(R2) convention regarding the creation of the ‘Worldwide unique case identification number’ (ICH-E2B(R2) A.1.10).	<p>The case should not be nullified.</p> <p>The ‘Sender’s (case) safety report unique identifier’ (ICH-E2B(R2) A.1.0.1) can be updated on the basis of the new primary source country code. However, the ‘Worldwide unique case identification</p>

Ex.	Scenario	Action
		<p>number' (ICH-E2B(R2) A.1.10) should remain unchanged.</p> <p>If, for some technical reason, the sender's local system is not fully ICH-E2B(R2) compliant and cannot follow this policy, then the sender should nullify the original case. A new case should be created with a new 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) reflecting the changed primary source country code. The 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) of the case that was nullified should be reflected in the data elements 'Other case identifiers in previous transmissions' (ICH-E2B(R2) A.1.11).</p>
12	<p>The suspected medicinal product belongs to another marketing authorisation holder (e.g. a product with the same active substance but marketed under a different invented name).</p>	<p>The case should not be nullified.</p> <p>It is recommended that the initial sender informs the other marketing authorisation holder about this case (including the 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10) used). The original organisation should also submit a</p>

Ex.	Scenario	Action
		<p>follow-up report to provide this new information.</p> <p>The other concerned marketing authorisation holder should create a new case and specify the reference case number and the name of the initial sending marketing authorisation holder in the data elements 'Source(s) of the case identifier (e.g. name of the company name of regulatory agency)' (ICH-E2B(R2) A.1.11.1) and 'Case identifier(s)' (ICH-E2B(R2) A.1.11.2). This will allow grouping the cases in the Pharmacovigilance database.</p>
13	<p>The suspected medicinal product taken does not belong to the marketing authorisation holder (same active substance, the invented name is unknown and the report originates from a country, where the marketing authorisation holder has no marketing authorisation for the medicinal product in question).</p>	<p>The case should not be nullified.</p> <p>The marketing authorisation holder should submit a follow-up report with this information within the appropriate time frame.</p>

Ex.	Scenario	Action
14	The case is mistakenly reported by the marketing authorisation holder A although the marketing authorisation holder B as co-marketer is responsible for reporting the case.	<p>The case should not be nullified.</p> <p>An explanation should be sent by the marketing authorisation holder A to the co-marketer marketing authorisation holder B that the case has already been reported. The marketing authorisation holder B should provide any additional information on the case as a follow-up report with the same 'Worldwide unique case identification number' (ICH-E2B(R2) A.1.10).</p>

Table VI.5. Process description - Data quality monitoring of ICSRs transmitted electronically

The business map and process description describe a system where there is a separation between a Pharmacovigilance DataBase (PhV DB) holder, the PhV DB holder's data Quality Assessors (QA) and the PhV DB holder's auditors; however this is not mandatory and these functions may be performed by the same people or groups.

No.	Step	Description	Responsible Organisation
1	Start. Decide upon Sender to evaluate.	Select one of the organisations that has transmitted ICSRs to your database. Inputs into this decision can include, but need not be limited to findings from previous assessments and requests from pharmacovigilance audits.	PhV DB holder
2	Sample ICSRs from Sender.	Take a sample of ICSRs that were transmitted by the selected sender	QA
3	Check for data quality errors.	Check the cases for data quality errors. The cases should be assessed against appropriate published standards and similar documents, for example the MedDRA Term Selection Points to Consider document.	QA
4	Write report and send to PhV DB holder.	The findings from the data quality assessment should be collated into a single report. These can include related checks, such as 15-day reporting compliance, whether error reports are corrected and similar statistical information.	QA
5	Errors found?	Were any errors found during the analysis of the cases? If No, go to step 5.1.	PhV DB holder

No.	Step	Description	Responsible Organisation
		If Yes go to steps 5.2, 5.3 & 6.	
5.1	End.	<p>If there were no errors found, then no further action needs to be taken. The process can end until the next time the sender is assessed.</p> <p>The pharmacovigilance database (PhV DB) holder may choose to share this information with the assessed sender and their auditors who may wish to factor this in to determinations of which sender to assess.</p>	PhV DB holder
5.2	Highlight for PhV audit.	If the PhV DB holder's organisation has an audit department, any significant findings should always be shared with them.	PhV DB holder
5.2.1	Prioritise for Audit.	The audit or inspections department should use the information provided to them to feed into decisions about prioritising organisations for audit or inspection.	PhV DB holder's auditors
5.3	INPUT: Findings from previous assessments.	Any errors found (or even lack thereof) should be incorporated into decisions about which senders to evaluate & should also inform the performance of the assessments (e.g. targeting particular types of case)	PhV DB holder

No.	Step	Description	Responsible Organisation
		and the report (documenting whether previously identified issues have been addressed).	
6	Inform sender of findings.	Inform the sender of the findings, including requested remedial actions (e.g. retransmitting certain cases) and time frames for those actions	PhV DB holder
7	Request meeting?	The sender should have the option to choose to request a meeting to discuss the findings and appropriate remedial action and time frames. If no meeting is requested, go to step 7.1. If a meeting is requested go to step 8.	Sender
7.1	Address the findings & retransmit any required cases.	Address all findings, take necessary steps to prevent recurrence of such findings & retransmit any required cases.	Sender
7.2	End.	Once all findings have been addressed, the necessary steps taken to prevent recurrence of such findings and any required cases have been retransmitted, the process can end until the next time the sender is assessed.	Sender

No.	Step	Description	Responsible Organisation
8	Have meeting.	Upon request from one party, a meeting should be held to discuss the findings of quality assessments and appropriate remedial and preventive actions to ensure that the cases in the database are correct and shall be so in the future.	PhV holder & DB Sender
9	End.	Unless further action has been specified (e.g. future meetings or assessments), the process can end until the next time the sender is assessed.	PhV holder DB

VI. Appendix 4: Duplicate detection and management of ICSRs

Figure VI.4. Business process map - Duplicate detection and management of ICSRs

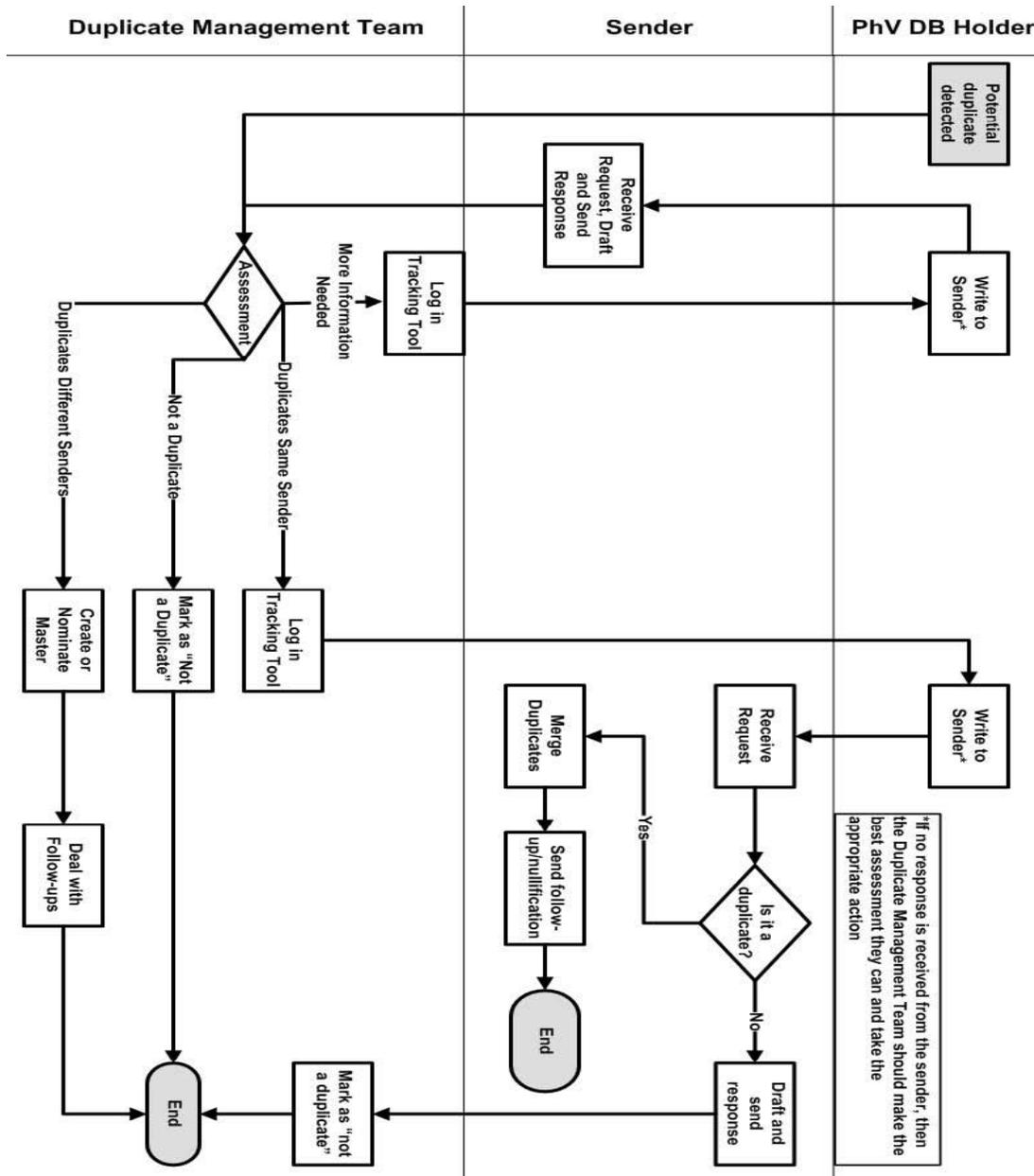


Table VI.6. Process description - Duplicate detection and management of ICSRs

DTM: Duplicate management team

No.	Step	Description	Responsible Organisation
1	Start. Potential duplicate detected.	Potential duplicates have been detected by the Pharmacovigilance Database (PhV DB) holder organisation or the PhV DB holder organisation is notified of potential duplicates by a receiver of the cases.	PhV DB holder
2	Assessment.	<p>All potential duplicates need assessment by the organisation Duplicate Management Team (DMT) to confirm or deny their duplicate status.</p> <p>Following assessment there are 4 possible outcomes:</p> <p>Not a Duplicate (go to step 2.1),</p> <p>More Information Needed (go to step 2.2),</p> <p>Duplicates From Different Sender (go to step 2.3),</p> <p>Duplicates From Same Sender (go to step 2.4).</p> <p>The outcome of all assessments should be recorded to avoid continually reassessing the same cases when further versions arrive. These recorded outcomes can also be used to refine the duplicate detection methods during future development.</p>	DMT

No.	Step	Description	Responsible Organisation
2.1	Not a Duplicate: Mark as not a duplicate.	If the cases are assessed as not being duplicates of one another, then mark both cases as such. Go to step 3 (End).	DMT
2.2	More information needed: Log in tracking tool.	There should be some form of tool for tracking when more information is needed, when correspondence has been sent, whether an answer was received and, if so, when.	DMT
2.2.1	Write to Sender.	More information is required in order to be able to make a definite assessment. The sender (who transmitted the case(s) in question to the PhVDB holder's organisation) should be contacted to request specific information necessary to confirm or deny duplication. Personal data protection must remain paramount, so unsecured communications should not include sufficient data to identify an individual.	PhV DB holder
2.2.2	Receive request, draft and send response.	Once a request for more information has been received, the Sender of the case should respond promptly, either as a follow-up version of the case or by responding to the requester.	Sender

No.	Step	Description	Responsible Organisation
		The DMT should then reassess the case based on the new information (Go back to step 2).	
2.3	Duplicates Different Senders: Create or nominate master.	Once cases have been determined to be duplicates of one another and have been transmitted to the PhV DB holder by different senders or reporters, then they should be merged under a master case, following the process described in chapter 2.3 “Management of duplicate cases” of the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs). This is an EMA guideline which is adopted in the SFDA from the scientific point of view.	DMT
2.3.1	Deal with follow-ups.	If any follow-ups arrive for any of the cases, this information may require a reassessment of the master case. Reassess and, if necessary, amend the master case as with any received follow-up information. Go to step 3 (End).	DMT
2.4	Duplicates Same Sender:	Once cases have been determined to be duplicates of one another, and have been transmitted to the PhV DB holder by the same sender, then this decision and	DMT

No.	Step	Description	Responsible Organisation
	Log in tracking tool.	the correspondence referred to in step 2.4.1 should be logged in the tracking tool referred to in step 2.2.	
2.4.1	Write to Sender.	<p>The sender organisation, as the source of the duplicates, should be contacted in accordance with chapter 2.3.3 of the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009 , (see GVP Annex III). This is an EMA guideline which is adopted in the SFDA from the scientific point of view.</p> <p>The sender should be asked to confirm or deny duplication and take appropriate steps in accordance with chapter 2.3.1 of the aforementioned Guideline.</p>	PhV DB holder
2.4.2	Receive request.	Receive and log the communication containing information on suspected duplicates in the Sender's PhV DB.	Sender
2.4.3	Is it a duplicate?	<p>Assess the potential duplicates. Are the cases duplicates of one another?</p> <p>If Yes, go to step 2.4.3.1.</p> <p>If No, go to step 2.4.3.2.</p>	Sender

No.	Step	Description	Responsible Organisation
2.4.3.1	Merge duplicates.	Merge the duplicates, taking into account Flowchart 1 of chapter 2.3.1.3 of the Guideline on the Detection and Management of Duplicate Individual Cases and Individual Case Safety Reports (ICSRs), EMA/13432/2009, (see GVP Annex III). This is an EMA guideline which is adopted in the Arab Countries from the scientific point of view.	Sender
2.4.3.1.1	Send follow-up /nullification	For the cases that are merged under the master, send a nullification message to the PhV DB holder. For the case that is master, send the updated case to the PhV DB holder as follow-up information. The merging & transmission should be completed promptly and in any case within 15 days of the date of receipt of the information from the PhV DB holder that the cases were considered to be possible duplicates. This date should be treated as the date of receipt of most recent information for regulatory reporting purposes.	Sender
2.4.3.1.2	End.	The duplicates have now been removed from both the Sender's system and that of the PhV DB holder and only the master should be available for signal detection and data quality analyses.	Sender

No.	Step	Description	Responsible Organisation
		Unless follow-up information is received, then no further steps need be taken.	
2.4.3.2	Draft and send a response.	Reply to the PhV DB holder who sent the communication informing that the cases are not duplicates.	Sender
2.4.3.2.1	Mark as “Not a duplicate”.	Upon receipt of confirmation from the Sender organisation that the cases are not duplicates, mark the cases as “Not a duplicate” & go to step 3 (End).	DMT
3	End.	No further action is required for this couple.	DMT

Annex 3

ART IV

Guidelines on The Conduct of Pharmacovigilance for Vaccines for Pre- and Post-Exposure Prophylaxis Against Infectious Diseases

1. Introduction

This guideline is addressed to MAHs and the SFDA. It should be read in conjunction with the other pharmacovigilance guidelines contained in this documents of the Rules Governing medicinal products in the KSA and provides additional guidance on the safety surveillance of vaccines used for the prevention against infectious diseases before or after exposure to an infectious agent.

This guidance takes into account the relevant specific aspects of vaccines, such as the balance between risks for the healthy vaccinee and the benefits for that individual as well as the whole population and side-effects due to the activation of the immune system.

Immunisation is one of the most effective and widely used public health interventions. The benefit of vaccination has been demonstrated for authorised vaccines, both at individual as well as community level. Prominent examples are the eradication of small pox and polio in most parts of the world. No vaccine is however 100% safe or effective. As the incidence of vaccine preventable diseases is reduced by increasing coverage with the efficacious vaccine, vaccine-related adverse events, whether causally related or perceived as such, become increasingly prominent.

Vaccines are different from most other medicinal products in ways that influence safety considerations. Vaccines are a preventive measure, usually given to healthy individuals and especially young children at vulnerable age. They have a complex composition and a short duration of exposure with a long-term response. No (immediate) health benefit might be apparent to the individual vaccinee due to the success of vaccines in reducing illness in the community. As a consequence, there is limited acceptance of any potential risks. Any safety concern arising with a vaccine might impact on a significant number of subjects. Therefore, safety concerns need to be promptly evaluated. As vaccines are often used in several birth cohorts or even in the whole population, events inadvertently occur in temporal but not in causal association to vaccination. Perceived safety concerns have been increasingly discussed in the public area. Public confidence in vaccination programmes may only be maintained if it is considered that the SFDA will assess the safety of vaccines in a timely and adequate manner and take appropriate action. This includes investigation of rare and unexpected adverse events, increases in the occurrence of known adverse reactions and careful analysis of theoretical concerns.

2. Scope

This guidance is addressed to MAHs and the SFDA. It should be read in conjunction with other pharmacovigilance guidance and is not intended to replace any other relevant guidance. This guidance mainly covers post-authorisation aspects specific for vaccines. Special attention is paid to the development of Risk Management Plans prior and after marketing authorisation. The guidance is directed to Applicants/MAHs and the SFDA and also aims at providing guidance to other stakeholders (e.g. sponsors of clinical studies, Healthcare Professionals, public health authorities) who are expected to use the guidance and thereby strengthen the cooperation of all stakeholders.

The guidance outlines the special considerations for pharmacovigilance of vaccines used in all age groups for pre- or post-exposure prophylaxis of infectious diseases. It is not intended to cover therapeutic vaccines (e.g. viral-vector based gene therapy, tumour vaccines, anti-idiotypic vaccines such as monoclonal antibodies used as immunogens), as these will require different considerations.

3. Roles and Responsibilities of Different Stakeholders

Stakeholders involved in the process of vaccine pharmacovigilance include the vaccinee and, in the case of paediatric vaccination, their parents/carers, Healthcare Professionals, Applicants/MAHs, sponsors of clinical trials, the SFDA and public health authorities recommending vaccination programmes and the World Health Organization (WHO). Depending on their responsibility, each stakeholder may have an important role in contributing to this process. Media has an important role in unbiased communication in particular in situations where there is a gap between the scientific analysis of experts and public perception of perceived risks which is especially relevant to vaccines.

4. Key Factors Contributing to Safety Profiles of Vaccines

4.1. Vaccine-Intrinsic Factors

4.1.1. Type of Vaccine

The safety profile of live virus or bacterial attenuated vaccines and inactivated vaccines (including vaccines based on bacterial proteins, polysaccharides or protein-conjugated

polysaccharides and recombinant protein vaccines) may have different safety profiles. Safety concerns associated with different types of vaccines identified prior to marketing authorisation should be investigated in the pre-authorisation phase and addressed in the Risk Management Plan (RMP). For concerns identified during the post-authorisation phase, appropriate safety investigations may be necessary. Both also apply to safety concerns which arise from experience with similar vaccines. Certain attenuated virus vaccine strains may be associated with adverse reactions usually seen with wild type virus. The level of attenuation and the possible impact on safety should be discussed in the Safety Specification of the RMP. If necessary, targeted post-authorisation safety studies (PASS) should be conducted.

Reversion to virulence after multiplication in the human host might be of particular concern for some live attenuated vaccines. Careful investigation of cases indicating a possible reversion to virulence in the post-authorisation phase is essential, especially for new live attenuated vaccines.

Validated and standardised assays, including assays to distinguish between wild and vaccine strains, should be developed and implemented prior to marketing authorisation for appropriate case assessment. Post-authorisation studies should also address, if relevant, the pattern of shedding, transmissibility to contacts and the potential of the strain to survive in the environment.

In rare occasions, some live attenuated vaccines may cause serious syndromes closely resembling wild-type disease, probably not associated with the vaccine but with individual host factors increasing susceptibility. Host risk factors such as age, gender and immune status of the vaccine should be carefully investigated. Clinical, serological and immunochemical analysis as well as virus detection, quantification, sequence analysis and cytokine release, may be helpful to further investigate the immune response elicited in the individual cases. Close collaboration with reference laboratories or specialised laboratories is recommended.

4.1.2. Immunogenic Adjuvants, Stabilisers, Preservatives and Residual Material from the Manufacturing Process

Incorporation of a particular adjuvant into vaccine formulations to enhance immunogenicity may be linked with induction of both local and systemic adverse reactions. Use of (novel) adjuvants targeted at stimulating a specific immune response justify particular attention to specific issues such as autoimmune diseases and rare and/or delayed onset adverse reactions. The clinical impact of the adjuvant in respect to impairing the immune response toward a Th2 (helper T-cell type 2)- response (as known for aluminium-based adjuvants) should be investigated in the postauthorisation phase. Synergistic immune-mediated reactions of adjuvants and the biologically active antigen should be considered.

Whereas currently used adjuvants are mainly aluminium salts and oil-in-water emulsions, a greater emphasis by vaccine manufacturers is now placed on discovery, development and testing of novel adjuvants for use, with the possibility of the occurrence of new safety concerns. The immunological mode of action of any novel adjuvants should be addressed in the pharmacovigilance specification of the Risk Management Plan. Where deemed necessary, post-authorisation safety studies (PASS) investigating potential rare and delayed onset effects of new adjuvants should be conducted. Cells from human, animal, insect, bacterial or yeast origin may be used in an early step of the manufacturing process. As a consequence, residual proteins of the host cells may be present in the final product. These impurities may consist of proteins that have structural homology with human proteins. In addition to extensive pre-clinical and clinical testing, post-authorisation surveillance may be appropriate to demonstrate that these residuals do not cause harm to vaccinees. Preservatives and stabilisers may not be as immunologically inert as previously thought (e.g. polygeline).

Removal of a preservative and/or stabiliser from a well-established vaccine may also have an impact on the safety profile of the vaccine as seen with a recent tick-bone encephalitis

vaccine. It is important to analyse whether the antigen itself or any ingredient has caused the adverse reaction. If necessary, risk minimisation strategies need to be explored.

4.1.3. Combined Vaccines

Combined vaccines consist of two or more vaccine antigens in one pharmaceutical preparation, intended to prevent multiple diseases or to prevent one disease caused by different serotypes. Possible safety concerns such as increased frequency of known adverse reactions (local or systemic) or increase of severity of adverse reactions should be carefully followed up. In the preauthorisation phase, it is only feasible to detect large differences in the incidence and severity of common adverse reactions between the combined vaccine and the precursor vaccine(s), whereas smaller differences of local or systemic adverse reactions are usually not detected in preauthorisation studies. Therefore, pharmacovigilance for combined vaccines should focus on a possible increase in the frequency and severity of local and systemic adverse reactions which might translate into tolerability of the vaccine. If appropriate, risk minimising strategies might be explored (e.g. preventive anti-pyretic treatment in small children).

4.1.4. Novel Vaccines

Where new approaches and novel concepts (e.g. temperature selected mutants), new technologies (e.g. vaccines using novel delivery systems), novel adjuvants or alternative routes of administration (e.g. nasal administration) have recently been developed or are currently in the clinical testing phase and may give rise to new safety concerns. Targeted monitoring and special studies are required for certain types of rare but serious adverse reactions. These may be anticipated from the particular composition of the novel vaccine or from their relatedness to well-established vaccines. Particular consideration should be given to what methods may be employed to detect long-term, delayed onset and, in case of vaccines for infants, developmental adverse reactions (see Chapter I.7).

4.1.5. Batch-Relatedness of Adverse Reactions

Manufacturing of medicines in biological systems, such as fermentation of bacteria, growth of virus in cell culture or expression of proteins by recombinant technology may introduce

variability within certain limits of the composition of the final product which may have impact on safety of the vaccine.

In principle, contamination with unwanted infectious agents at many different points, as well as generating aberrant materials cannot be totally excluded. Although a great deal of effort is put into control of raw and starting materials and the manufacturing process as well as testing of each single batch to exclude contamination with infectious agents and other risks linked to any aberrant material, these potential risks which may result in adverse reactions should be considered. As these adverse reactions may be related to certain batches, pharmacovigilance systems should be capable of recording individual lots.

If there is reasonable suspicion of an association between the occurrence of adverse reactions and a particular batch of a vaccine, the SFDA should be informed immediately by the MAH. A full assessment of the possible reason for batch-relatedness of adverse reactions needs to be provided. Where a quality defect is suspected or confirmed, the SFDA should be informed immediately by the MAH.

4.1.6. Vaccination Schedule and Route of Administration

Different immunisation schedules may impact on the safety profile of a given product. The pharmacovigilance plans of the Risk Management Plan, study designs and causality assessments should be focused as appropriate, drawing from prior experience (e.g. incidence and severity of limb swelling with subsequent doses of DtaP (Diphtheria, Tetanus and Pertussis-acellular) vaccine).

The vaccine administration route is known to be another important factor influencing safety of a vaccine. Potential implications need to be considered, in particular for alternative routes of administration (e.g. intranasal, oral, intradermal). The impact of adjuvants needs to be explored.

4.2. Host Factors

4.2.1. Special Age Groups

Immunological responses to vaccines depend on the independent and coordinated function of innate and adaptive immune responses which is different in young children, young adults and elderly persons. Differences of the immune response in different age categories may not only translate to different efficacy of vaccines, but also to differences in the safety profile. Adverse reactions may occur solely in certain age categories, e.g. hypotonic hyporesponsive episode (HHE) in young children. Furthermore, the frequency of adverse reactions may change in relation to age.

Targeted surveillance of adverse reactions in different age groups is warranted. Prior to marketing authorization it may not be possible to study all aspects of age related safety issues for a new vaccine. Therefore, these aspects may be addressed in the Risk Management Plan, if relevant.

4.2.2. Pregnancy

Although, most live attenuated vaccines are contraindicated in pregnant women due to the known or suspected risk of transplacental infection of the foetus, inadvertent exposure during pregnancy cannot be avoided. Risk to the developing foetus from vaccination of the mother with an inactivated virus, bacterial or toxoid vaccine during pregnancy is considered theoretical and should be further investigated on the basis of data collected in the post-authorisation phase. This may range from follow-up of spontaneously reported pregnancies up to additional pharmacovigilance activities such as pregnancy register (in particular if a new adjuvant is used). The detailed design of the preferred approach to collect such data should be provided as part of the Risk Management Plan. The studies should be designed to identify spontaneous abortions, stillbirths and congenital malformations.

Adequate duration of follow-up of the offspring should be guaranteed. Detailed information on vaccine exposure (including number of doses and gestational age at the time of exposure) before and/or during pregnancy is warranted. Documentation and investigation should also include other risk factors. Pregnancy registers which are already

available may be capable of providing the necessary data. Careful monitoring and follow-up of reported pregnancies is necessary for all vaccines.

4.2.3. Immunocompromised Individuals and HIV-Infected Persons

Immunocompromised individuals may not only be very sensitive to serious disease after exposure with the natural infectious agents, but may also be very sensitive to the occurrence of serious adverse reactions.

5. Risk Management Plan

As most aspects of existing RMP guidance is equally applicable to medicines and vaccines, this section should be read in conjunction with the Rules Governing medicinal products in the KSA. That section provides guidance on some issues specific for vaccines.

5.1. Safety Specification

5.1.1. Pre-Clinical Aspects for Further Consideration

Safety concerns for a vaccine include those due to inherent toxicities of the antigen and adjuvant, toxicities of impurities and contaminants and toxicities due to interactions of the vaccine components present in the vaccine formulation.

If findings from pre-clinical testing with a possible impact on safety and/or serious adverse reactions possibly related to the investigated vaccine occur, there may be a need to extend the safety database in the post-authorisation phase in order to ensure that the pre-clinical findings do not translate into a risk in humans (e.g. potential concern of enhanced pathology in small children to subsequent infections after whole viral inactivated aluminium adjuvanted vaccines).

5.1.2. Limitation of the Safety Database and Population Not Studied in the Pre-Authorisation Phase

Serious and clinically relevant adverse reactions are mostly rare and thus are unlikely detected prior to marketing as the sample size of clinical trial database is mostly limited to detect common and uncommon adverse events. Long-term follow-up of vaccinees might also be limited and preauthorization data will most likely not address concerns of long-

term risks. Furthermore, in preauthorization clinical trials the study population is highly selected, whereas in the postauthorisation phase immunisation might be targeted at a heterogeneous population with diverse background diseases.

5.1.3. Potential Risks Requiring Further Investigation

Experience with similar antigens, types of antigen and/or other adjuvants and other vaccine excipients should be described in the RMP. The impact of adjuvants, stabilisers, preservatives or residuals of the manufacturing process should be discussed in the RMP. Safety concerns anticipated from experience with similar vaccines and vaccine ingredients should be addressed in the RMP and, if necessary, a commitment to undertake post-authorisation safety studies should be provided. Safety parameters based on biological plausibility of the occurrence of certain adverse reactions or previous experience with a similar authorised vaccine should be investigated in detail. It should be considered whether more additional information (e.g. cytokine profiles) might be of value.

5.1.4. Identified and Potential Interactions

Emphasis should be placed on identified and potential interactions with co-administration of other vaccines. This should include a prospective specification based on issues with likely concomitant use in the KSA such as higher reactogenicity of concomitant vaccination and clinically relevant immunological interference. Past experience with similar vaccines and types of antigens should be considered.

If clinical trials or literature data indicate potential interactions with medicinal products usually given to the target population or administered as a prophylactic treatment (e.g. antipyretics in order to minimise adverse reactions) adequate investigations in the post-authorisation phase might be warranted.

5.1.5. Epidemiology of the Target Disease and Background Incidence of Adverse Events of Interest

This section of the RMP should focus on the different natural histories of the target disease in the KSA as appropriate and highlight any particular considerations required. The section should discuss any relevant examples of impact of previous and similar vaccines on the

disease and any potential concerns to monitor. For vaccines that may protect against only some types of organisms within a species, appropriate surveillance should be in place to detect strain replacement phenomena. Emphasis should be given on assessing the population and age-specific background rates of adverse events of special interest in order to assist evaluation of spontaneous reports of adverse reactions.

5.1.6. Potential of Transmission of Infectious Agents

The RMP should address for live attenuated vaccines aspects such as shedding, transmission of the attenuated agents to close contacts, risk for pregnant women and the foetus, and reversion to virulence (see Chapter I.5).

As for all biological products, the potential for infections caused by residuals of biological material used in the manufacturing process as well as contaminations introduced by the manufacturing process should be evaluated and addressed in the RMP.

5.2. Pharmacovigilance Plan

This section of the RMP is covered by Chapter I.3 in general terms. There are special considerations for both routine and additional pharmacovigilance activities for vaccines such as the need to investigate serious but rare adverse reactions (even if the sole aim is to provide reassurance on safety), batch-related adverse reactions, if appropriate, safety of concomitant vaccination and evaluation of the impact of different immunisation schedules. Different policies on use of vaccines concerning vaccination schedules and target population might give rise to different safety issues. If a specific safety concern associated with the vaccination schedule or the target population can be anticipated from other vaccines, targeted postauthorisation studies should be considered.

At the time of marketing authorisation, data on long-term duration of protection, the potential for waning immunity and the need for a booster dose are usually not available. Plans for collecting these data should be presented as part of the RMP.

MAHs should explore availability of systems for collecting data in different countries, particularly when addressing specific safety concerns. Pharmacovigilance methods with regard to data collection and signal detection and evaluation are further explored in Chapters I.7 and I.8.3.

5.3. Risk Minimisation

Risk minimisation measures for vaccines are considered to be the same as for other medicinal products (see Chapter I.3).

6. Data Collection

6.1. Adverse Events Following Immunisation (AEFIs) and Adverse Reactions

Adverse Events Following Immunisation (AEFIs) are clinical observations of adverse nature in vaccinees, and they may be classified as occurring:

1. in suspected causal relationship with the vaccination; or
2. coincidentally after vaccination.

Those AEFIs which are suspected to occur in causal relationship with the vaccination represent suspected adverse reactions and may be further classified as follows:

1. Vaccine-related
 - 1.a due to the intrinsic characteristics of the vaccine as formulated;
 - 1.b due to a quality defect of the vaccine;
2. Vaccination error (e.g. use not as authorised, prescription error, storage error, dispensing error, administration error);
3. Vaccination anxiety (e.g. syncope).

Vaccines are intended to have powerful effects on the immune system. It is understandable therefore that healthcare professionals and the public may perceive adverse events

occurring in temporal association with vaccination as causally related, even if no causal link exists. AEFIs might be reported to the SFDA as well as MAHs as spontaneous reports.

6.1.1. Suspected Adverse Reactions

Spontaneously reported suspected adverse reactions remain an important source for the detection of safety issues in the post- authorisation phase, in particular with regard to rare, serious adverse reactions with a low background event rate. Spontaneous reporting is also useful to cover safety aspects in the diverse populations. Different types of adverse reactions should be considered:

- those that are perceived as adverse reactions, but may be visible signs of the immune response of the host (interleukine response, e.g. fever);
- those reflecting the clinical picture of the disease for which immunisation has been given (e.g. measles-like rash following vaccination); and
- those that are unexpected and for which a causal relationship remains to be elucidated.

For assessment of individual case reports of suspected adverse reactions, it is essential that complete and accurate records documenting administration of all vaccines, together with information on the date of vaccination, product administered, manufacturer, batch number, site and route of administration, detailed description and course of the adverse event/reaction as well as therapeutic intervention are provided. Appropriate follow-up of serious suspected adverse reactions is of inherent importance including data on possible alternative causes of the adverse event. It may be helpful to develop predefined check lists or formats for those reactions which may be anticipated from experience with similar vaccines for reporting in the post-authorisation phase in order to ascertain consistently relevant clinical information to ensure the quality of the causality

assessment of an individual case. Standardised case definitions of adverse events are a key element for scientific assessment of immunisation safety as they provide a common terminology and understanding of adverse events/reactions and thus allow for

comparability of data. Case definitions of the Brighton Collaboratio(16) should be used, if appropriate. Several aspects need to be considered when assessing single cases of suspected adverse reactions.

- The population of vaccinees is usually large and heterogeneous and coincident adverse events are likely to occur.
- In addition to the intended active ingredient, the antigen, additives and excipients for production - inactivation, preservation, and stabilisation of vaccines also play an important role in evaluating the causal relationship of a suspected adverse reaction with a given vaccine.
- Categories or algorithms used for causality assessment for medicinal products might not be equally applicable for vaccines. There might be a need to adopt the categories to vaccines.

This should be stated in the RMP. The currently ongoing work of the Joint Council for International Organizations of Medical Sciences (CIOMS)/WHO Working Group on Vaccine Pharmacovigilance should be regarded in this respect. De-challenge and reexposure testing which are important criteria for several causality are mostly not applicable to vaccines.

6.1.2. Vaccine Failures

Most vaccines are not 100% effective. Therefore cases of breakthrough infections are expected. A higher-than-expected efficacy of a vaccine, waning efficacy over time or replacement phenomenon cannot be fully investigated via spontaneous reporting. Nevertheless, expedited reporting is recommended. Risk factors for vaccine failure should be analysed (e.g. obesity, age, smoking status, vaccination schedule, concomitant disease). This may provide signals for reduced immunogenicity of the vaccine under daily life conditions in risk groups. If there is concern that a higher than expected rate of vaccine failures and break-through infections in certain risk groups exists, appropriate systematic investigations should be carried out. Appropriate case definitions and validated analytical tests for confirmation of the infective agents should be used. Case definitions for vaccine

failure, lack of effect, break-through infection are not universally agreed at present, but it is expected that consistent case definitions will be published in the near future by the Joint CIOMS/WHO Working Group on Vaccine Pharmacovigilance. Vaccination failure should be defined in the RMP.

6.1.3. Vaccination Errors

Inappropriate handling may lead to infection, bacterial contamination, blood-borne infection and abscess formation. These issues apply particularly to multi-dose container vaccines without preservatives. For some vaccines, the method of administration may be associated with adverse reactions and this should be considered when assessing a single case report of a suspected adverse reaction.

MAHs should adequately follow-up the root cause of any errors (e.g. cold chain investigation, batch investigation) and address this appropriately through communication. The potential for and risk minimisation actions addressing such errors need to be described in the RMP. It is of inherent importance to measure outcome of the actions taken.

6.2. Periodic Safety Update Reports (PSURs)

In addition to information which should be provided in the Periodic Safety Update Report (PSUR) for all medicinal products (see Chapter I.6), special consideration should be given in PSURs for vaccines to any potential impact on safety of major as well as minor changes in the manufacturing process. Issues related to batch(es), as well as age-related adverse reactions should be evaluated. Safety aspects in subpopulations (such as pregnant women) should be analysed. If relevant, the reactogenicity of a vaccine should be analysed for different doses of the vaccine schedule and also across different vaccination schedules.

Reports of vaccine failure / lack of efficacy should be assessed in a separate chapter of the PSUR. Vaccination errors and vaccination anxiety-related reactions such as syncope should also be summarised and analysed in the PSUR. Actions taken to avoid vaccination errors may be described in the PSUR. In accordance with Chapter I.6, relevant published data on safety should be presented in the PSUR. Literature data should not solely focus on

safety information available for the antigen(s), but should also summarise published information relevant for other vaccine components such as stabilisers, preservatives and adjuvants.

If concomitant vaccination with another vaccine is specifically mentioned in the Summary of Product Characteristics (SPC), safety aspects identified with co-administered vaccines should be analysed separately and summarised in the PSUR.

6.3. Post-Authorisation Safety Studies (PASS)

As rare but serious adverse reactions, reactions with delayed onset and reactions in sub-populations are usually not detected prior to marketing authorisation post-authorisation evaluation of safety in studies is critical for vaccines. Safety concerns arising during the post authorisation may relate to:

- the increased incidence of a natural disease;
- vaccine specific adverse reactions;
- a higher rate of expected adverse reactions compared to comparators or precursor vaccines.

Certain aspects of post-authorisation safety studies (PASS) may be of particular interest:

- those aiming to confirm that the safety profile is acceptable under real life conditions (large numbers of patients studied with the aim of expanding the safety database, pro-active safety testing);
- those aiming to evaluate new safety issues including perceived risks ad hoc;
- those intended to evaluate known or expected safety concerns (e.g. those detected in the pre-authorisation phase and those anticipated from other similar vaccines);
- those aimed at providing laboratory confirmation of a causal link; and
- those aimed at investigating the aetiology of the adverse event/reaction.

For assessment of safety signals, controlled clinical trials and prospective cohort studies are considered to provide the highest level of evidence. Active surveillance of rare adverse reactions by follow-up of a cohort recruited at the time of vaccination requires follow-up

of a large number of vaccinees. Retrospective (i.e. historical) cohort studies may be conducted, since the group in whom the adverse events/reactions is studied is not defined at the time of vaccination but is defined retrospectively, according to the population-based data set available at the time the study is conducted.

In order to interpret the rates of the (various) disease(s) that will occur over time in the vaccinated cohort, an unvaccinated control group is also required, consisting of individuals born during the same period, recruited at the same age and followed up since recruitment through the same methods. However, this may not be feasible because of a large sample size needed. Furthermore, once a vaccination is recommended for use, it may not be possible to identify appropriate concurrent controls. In such cases, historical controls may be an option.

An alternative to clinical trials and cohort studies for the active surveillance of adverse events/reactions is the use of databases with computerised data sets of clinical diagnosis and information on immunisation records of a large number of individuals. Integrated databases such as the General Practice Research Database (GPRD) or IMS Health database or any similar local data base may be appropriate for epidemiological studies. By use of databases, studies may be conducted following different designs. Studying large populations may provide the opportunity to even study rare adverse events. A recently established method in this respect is the use of record linkage of computerised data sets (disease/diagnosis and immunisation records) from different databases using a unique patient identifier. Clinical diagnosis/disease data may be diverted from computerised hospital discharge data, computerised general practice records data or other clinical databases (insurance company database). Such linked data sets have been used for formally testing hypothesis raised by uncontrolled observations. When such linked data sets are trawled for statistically significant associations for which no a priori hypothesis was used, and if enough associations are sought, some will be considered statistically significant just by chance. Therefore, database studies should be interpreted with particular caution.

Caution should also be exercised if such database studies are used for generating hypotheses.

Computerised databases may also be used for conducting case-control studies. Vaccination histories of cases and controls may be compared in order to study the effect of vaccination on the risk of an adverse event/reaction and to study the effects of co-variables. This method allows for detection and assessment of risk factors and identification of vulnerable subgroups. It is ideal for rare events/reactions and for such reactions preferable to cohort studies. However, the limitations of such a study design needs to be acknowledged. This is in particular important for vaccines as

many serious adverse events are so rare that it is even difficult to study them in a case control design (e.g. anaphylactic reactions). Using the case-control approach in rare events, relative risk may reliably be estimated by odds ratios. Odds ratios may be adjusted for potential confounders by multivariate logistic regression. It is important to select controls appropriately, since selection bias in controls may potentially compromise representativeness and introduce a systematic error in effect estimates. Particularly in studies on vaccination, one has to expect potential confounding by health awareness, for example if subgroups are more or less likely to be immunised. In studies unable to adjust for such effects, odds ratios for immunisation effects may systematically over- or underestimate any true association.

To estimate an association between vaccination and adverse events, the self-controlled case-series (SCCS) design proposed by Farrington et al (*Am J Epidemiol.* 1996; 143:1165-1173) has been used in the past as it might to avoid biases in a case-control design when the coverage rate of immunization is high in universal vaccination programmes (lack of appropriate un-immunised control group). According to this study design, only vaccinated cases are included in the analysis. For each case, the observation period following each vaccine dose is divided into risk period(s) (the days immediately following each vaccination) and control period (the remaining observation period).

Incidence rates within the risk period after vaccination are compared with incidence rates within the control period, taking age, in particular, into account, under the null hypothesis, that incidence rates would be equivalent if no association with vaccination is present. An SCCS analysis has the advantage of an implicit control of any potential confounders, even when unknown, which are stable over time and may also control for age effects. For unique events, this method requires the additional assumption that the cumulative incidence of events in the population over the observed period is low. Data analyses may be performed early and time efficiently. Compared to cohort or case-control studies, an SCCS analysis tends to be faster and may be more feasible when examining rare events, as only information on cases is required. Besides these strengths, the SCCS method has some limitations.

Like cohort or case-control studies, the SCCS method remains susceptible to some bias if vaccination is timed to minimise the risk of an adverse event. In principle, the case series method is capable of estimating relative risks. Another problem is that a relevant time interval needs to be defined. Primary immunisation with several doses might result in problems of ascertainment of cases.

Ecological studies examine the correlation between the trends in an indicator of vaccine coverage and the trends in incidence of a disease that is a presumed effect of that vaccine. These trends can be examined over time or across geographical regions. In such analysis, it is hypothesised that a strong correlation between the two trends is consistent with a causal relationship, while a weak correlation would indicate a weak relationship. However, they compare data at the population level and not at the individual level and are unable to control for confounding variables and differentiate between true association and coincidence. Their results should therefore be interpreted with caution. Ecological studies may be useful to generate hypotheses.

Safety parameters in PASS should be appropriate for the specific study vaccine. A prerequisite is the use of globally accepted standards for case definitions (e.g. those published by the Brighton Collaboration (16) to compare the frequency of adverse reactions across

different studies. The possibility of meta-analysis of different studies for identification of rare adverse reactions should be discussed. Severity categories such as mild, moderate, and severe should be avoided.

Despite availability of the above mentioned tools, the difficulty of investigating possible long term risks which may only become evident several years or even decades after vaccination is acknowledged.

Experimental investigations should be considered in addition to address safety concerns including virological, bacteriological and/or immunological experiments and methods to elucidate the aetiology of an adverse reaction.

7. Data Evaluation

7.1. Signal Detection

Signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions may arise from any source including preclinical and clinical data (e.g. spontaneous reports from Healthcare Professionals or Consumers; epidemiological studies; clinical trials), published scientific and lay literature.

In databases containing spontaneous reports where incidence rates cannot be computed, the method of choice may be a measure of disproportionality, detecting a signal of disproportionate reporting (SDR). SDRs refer to a statistical association between medicinal products and adverse events. There are several statistical methods used to detect SDRs, such as the proportional reporting ratio (PRR) or Bayesian approaches.

Vaccines may require special consideration when applying such tools. Intrinsic differences between vaccines and other medicinal products should be considered, for example frequent reporting of unrelated adverse events in the target population (e.g. Sudden Infant Death Syndrome (SIDS) and childhood vaccination, myocardial infarction and flu vaccines). Furthermore, the safety profile of a vaccine may differ substantially among the target population (e.g. higher reactogenicity in younger vaccinees). In order to reduce background

noise, estimates of disproportionality should be calculated based on a comparison across groups that have a similar likelihood of experiencing similar adverse events. The choice of the comparator group will depend of the objectives of the analysis and the information available in the database. A comparison with all medicinal products may result in the detection of reactions specifically related to vaccines, but may also identify a high number of false signals (e.g. SIDS in infants) or already known mild and expected reactions (e.g. local reactions).

On the other hand, using all vaccine-related reports available in the database may result in signals of age related reactions (e.g. cardiac disorders if the vaccine of interest is used in the elderly). In a first step, it may therefore be appropriate to examine results of statistical methods using both comparator groups, or to use reports for other vaccines as the comparator group with a stratification made at least by age and seriousness. Given the large differences in reporting rates between regions, stratification by geographical region may also be considered. Stratification by comorbidity or comedication is desirable, but may be difficult to achieve. If Consumer/Patient reports of suspected adverse reactions are included in the database, signal detection should also be stratified by source (Healthcare Professionals, Consumers/Patients). Stratification between study reports and spontaneous reports is warranted. When stratification is performed, it may be wise to examine the results of both adjusted and non-adjusted analyses. Results should be inspected in each stratum as pooled result of a stratified analysis may miss signals.

Due to often universal vaccination policies, it is inevitable that coincidental events causing concerns will be reported in close temporal association with immunisation. There is therefore a need to assess the population and age-specific background rates of events of interest in order to assist evaluation of passive data. A simple method of investigating a signal is to compare the number of cases observed in temporal relationship to a suspected exposure during a period of time (O) to the number of natural incidences of the disease estimated to occur in the same period of time (E), assuming no relationship to the suspected exposure. Observed means usually reported via spontaneous reporting.

O/E analyses are the first level of evaluation of safety signals. A classical approach is to calculate the O/E ratio and determine if this ratio is significantly different from one.

Certain limitations of this analysis should be considered (e.g. underreporting, healthy vaccine effect). A robust calculation of the exposed population and the incidence of the natural disease are warranted. Usually, the classical O/E analysis does not account for variability of parameters that were used to estimate the expected number of cases, such as variability of the incidence of the event, the age distribution of the event and the age distribution of vaccination. As a consequence the approach is considered to be rather conservative.

Less conservative but more complex approaches have been developed recently. These approaches focus on E rather than on O/E and accounts for an age effect on E. In this analysis E is not a fixed number and O/E must be interpreted as a point estimate with variability around them.

Standardised MedDRA (Medical Dictionary for Regulatory Activities) Queries (SMQs) (3) may be used in the process of signal detection and evaluation. Sensitivity and specificity testing of SMQs for vaccines needs to be done beforehand in order to adequately interpret the results. Signal evaluation is of inherent importance. Case definitions as e.g. published by the Brighton Collaboration (16) may be used for signal validation. However, this needs to be justified on a case by case basis. When evaluating signals, the following potential biases should be taken into account (in addition to age and seriousness):

- vaccination policy (target group of subjects to be immunised);
- the incidence of natural disease in the target population;
- public information (public campaign, press) that may favour certain reports in some periods;
- seasonality.

Of note, a statistical association does not imply any kind of causal relationship between the administration of the vaccine and the occurrence of the adverse events.

7.2. Data Analysis

It is of inherent importance that data are managed in a form that allows data retrieval and analysis by age groups (e.g. premature infants, neonates, infants and the elderly), number of doses, different vaccination schedules, defined risk factors or underlying diseases and adverse event/reaction types.

Clusters of reported adverse events/reactions should be identified. The safety profile of a vaccine may vary across different batches, therefore retrieval by batch number is also necessary. The same holds true for changes which are introduced into the manufacturing process. Full traceability of all manufacturing changes and links to safety data should be ensured.

Key data to be collected and analysed (in addition to the data on the patient and the immunization history), are data about the vaccine and the diluent (if applicable) administered to the patient. Manufacturer(s), batch number(s), batch release specifications, expiry date(s), distribution data, storage conditions, and laboratory test results about the vaccine/batch, if appropriate. Distribution and administration -related data should also be collected and analysed, such as storage and handling conditions for vaccines in the healthcare institution where immunisation took place. This information may help identify products inappropriately used or patterns of error.

7.3. Risk Evaluation

The objectives of pharmacovigilance for vaccines are to identify rare or new adverse events, identify those that are causally related to the vaccine /vaccination and estimate their rate of occurrence. In addition, any change in the frequency or severity of a known safety concern requires prompt evaluation. Evidence of causality is based on biological plausibility supported by laboratory evidence and/or statistically significant excess of events in the post-vaccination period.

Passive reporting systems have methodological limitations, particular for ascertaining reliable adverse event/reaction rates and investigating causal relationship. Therefore, additional pharmacovigilance activities are required. Errors in manufacturing, handling

and administration should also be evaluated. Action to avoid such errors should be explored.

7.4. Risk-Benefit Assessment

The risk-benefit balance for vaccines depends largely on the incidence of the infectious disease in the target population, the proportion of infected persons with clinical disease, the severity of clinical disease as well as the risk of transmission, identification of high risk groups and geographical and seasonal characteristics of the infectious disease. For vaccines already included into the national vaccination programme, the impact of the vaccine on the epidemiology of the vaccine-preventable condition should be considered as well as the impact on individual protection.

Due to the success of vaccination programmes in their later stages, whether there is herd immunity as well as individual protection, the risk-benefit balance might change. Differences in morbidity and mortality of an infectious disease in different countries have to be considered.

8. Risk Minimisation and Regulatory Action

In principle, regulatory tools and risk minimisation activities for vaccines are similar to those of conventional medicinal products.

8.1. Precautionary Measures

There may be circumstances where scientific evidence is insufficient, inconclusive or uncertain and where there are reasonable grounds for concerns that the potentially dangerous effects may be inconsistent with the chosen level of protection. A decision to take measures without waiting until all the necessary scientific knowledge is available, may be particularly relevant for vaccines in special circumstances, e.g. vaccines for healthy children. Because the potential for any risk is considered less acceptable in the case of preventive vaccines than in the context of disease treatment, decision makers may respond to concerns which may be linked to vaccination despite uncertainties of scientific knowledge by taking precautionary measures.

8.2. Product Information

The guidance documents on the SPC available in the Saudi Guidelines for Development of Vaccines should be adhered to when evaluating proposed SPC wordings.

8.3. Risk Communication

As immunisation programmes in countries mature, incidence rates of the targeted diseases are substantially decreased by high vaccine coverage rate. The level of trust in immunisation is usually high at the beginning of an immunisation programme when the disease is frequent and Patients and Healthcare Professionals have personal experience with the disease. As immunisation programmes successfully reduce the incidence of vaccine-preventable diseases, an increasing proportion of vaccinees and Healthcare Professionals are removed from personal experience with the disease and consequently rely for on historical and other more distant descriptions. This situation markedly influences risk perception and in return real or perceived adverse effects of immunisation receive relatively more attention.

Risk perception may differ between stakeholders (Patients, Healthcare Professionals, scientists, vaccination programme officers, regulators), especially when there is uncertainty about a risk. Public confidence in vaccination programmes may only be maintained by the public knowledge that systems are in place to ensure a complete and rapid safety assessment and to take measures even on precautionary basis.

Communication of safety information is essential to respond to public concerns. Delivery of rapid, transparent, accurate and well-balanced information on the scientific evidence base is warranted. Communication to the public should be a collaborative undertaking between industry, regulators and public health organisations with input from all stakeholders. A key element is to clearly explain what is known about the safety and efficacy of a vaccine when it is first used in the population and what processes are in place for gathering additional safety data.

Communication may differ in different scenarios of vaccine use and with regard to different vaccines. It is essential to maintain a high level of transparency and to define the roles and responsibilities of each stakeholder in each phase.

8.4. Audit and Outcome Assessment

There is a need to ensure effective follow-up of the pharmacovigilance process and measurement of the outcomes of any actions taken. Actions taken, measures and methods as well as time-lines should be clearly described in the RMP.

Module VII – Periodic Safety Update Report

VII.A. Introduction

Periodic safety update reports (PSURs) are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase. All applicable legal requirements in this Module are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

The format of PSURs shall follow the structure described in the annex 1. This Module provides guidance on the preparation, submission and assessment of PSURs.

The scope, objectives, format and content of the PSUR are described in VII.B.. The required format and content of PSURs 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 format previously described in the ICH-E2C(R1). In the KSA, the report shall be described and named as PSUR.

Further details and guidance for the submission of PSURs in the KSA, including the frequency of submission are provided in VII.C.

Marketing authorisation holders should submit PSURs to the SFDA according to the following timelines:

- within 70 calendar days of the data lock point for PSURs covering intervals up to 12 months (including intervals of exactly 12 months); and
- within 90 calendar days of the data lock point for PSURs covering intervals in excess of 12 months;

- the timeline for the submission of ad hoc PSURs requested by the SFDA will normally be specified in the request, otherwise the ad hoc PSURs 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 should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation.

The obligations imposed in respect of PSURs should be proportionate to the risks posed by medicinal products. PSUR reporting should therefore be linked to the risk management plans (RMPs) of a medicinal product (see Module V). The “modular approach” of the PSUR described in VII.B.5. aims to minimise duplication and improve efficiency during the preparation and review of PSURs 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 utilised interchangeably across different PSURs, DSURs and RMPs.

The new legislation also waives the obligation to submit PSURs routinely for generic medicinal products well established use medicinal products, homeopathic medicinal products and traditional herbal medicinal products. For such products, PSURs shall be submitted where there is a condition in the marketing authorisation or when requested by the SFDA on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs for an active substance after its authorisation.

SFDA shall assess PSURs to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

As part of the assessment, it should be considered whether further investigations need to be carried out and whether any action concerning the marketing authorisations 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 finalisation of the ICH-E2C(R2) guideline on PBRER.

VII.B. Structures and processes

VII.B.1. Objectives of the periodic safety update report (PSUR)

The main objective of a PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits. The PSUR is therefore a tool for post-authorisation 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-authorisation phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorisation clinical trials. A different benefit-risk profile may emerge as pharmacovigilance reveals further information about safety. The marketing authorisation holder should therefore re-evaluate the risk-benefit balance of its own medicinal products in populations exposed. This structured evaluation should be undertaken in the context of ongoing pharmacovigilance (see Module XII, which will be realised) and risk management (see Module V) to facilitate optimisation of the risk-benefit balance through effective risk minimisation.

A PSUR 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 risk-benefit balance within PSURs 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 minimisation.

After a marketing authorisation 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 favourable.

The analysis of the risk-benefit balance should incorporate an evaluation of the safety, efficacy and effectiveness information that becomes available²⁶, 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 unauthorised 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 (e.g. use in paediatric population or in pregnant women). Sources of information on use outside authorisation may include drug utilisation 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 authorised indications. The integrated benefit-risk evaluation should be based on all authorised indications but should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorised indications).

The evaluation should involve:

²⁶ The ICH-E2C(R2) guideline should not serve to limit the scope of the information to be provided in the benefit-risk evaluation of a medicinal product. Please refer to the applicable laws and regulations in the KSA

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 summarising relevant new safety, efficacy and effectiveness information that could have an impact on the risk-benefit balance of the medicinal product.
3. Conducting an integrated benefit-risk analysis for all authorised indications based on the cumulative information available since the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country. For the cases where the DIBD is unknown or the marketing authorisation holder 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. Summarising any risk minimisation actions that may have been taken or implemented during the reporting interval, as well as risk minimisation 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 risk-benefit analysis, the marketing authorisation holder shall draw conclusions in the PSUR as to the need for changes and/or actions, including implications for the approved SPC for the product(s) for which the PSUR is submitted.

VII.B.3. Principles for the preparation of PSURs

Unless otherwise specified by the SFDA, the marketing authorisation holder shall prepare a single PSUR for all its medicinal products containing the same active substance with information covering all the authorised indications, route of administration, dosage forms

and dosing regimens, irrespective of whether authorised 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 and any safety concerns shall be addressed accordingly. There might be exceptional scenarios where the preparation of separate PSURs 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 authorisation. Case narratives shall be provided in the relevant risk evaluation section of the PSUR 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 individual case safety report (ICSR) but rather a clinical evaluation of important or illustrative cases in the context of the evaluation of the safety concern/signal.

The format and table of contents of all PSURs should include interval as well as cumulative data. As the PSUR 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 minimisation activities evaluated in the PSUR include updates to the product information.

The reference product information for the PSUR should include “core safety” and “authorised indications” components. In order to facilitate the assessment of benefit and risk-benefit balance by indication in the evaluation sections of the PSUR, the reference product information document should list all authorised indications in ICH countries or regions. When the PSUR is also submitted to other countries in which there are additional locally authorised indications, these indications may be either added to the reference product information or handled as a regional appendix as considered most appropriate by

the marketing authorization holder. The basis for the benefit evaluation should be the baseline important efficacy and effectiveness information summarised in the PSUR 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 marketing authorisation holders when selecting the most appropriate reference product information for a PSUR:

- Company core data sheet (CCDS) – It is common practice for marketing authorisation holders to prepare their own company core data sheet which covers data relating to safety, indications, dosing, pharmacology, and other information concerning the product. The core safety information contained within the CCDS is referred to as the company core safety information (CCSI). A practical option for the purpose of the PSUR is for each marketing authorisation holder to use the CCDS in effect at the end of the reporting interval, as reference product information for both the risk sections of the PSUR as well as the main authorised indications for which benefit is evaluated.

- When the CCDS does not contain information on authorised indications, the marketing authorisation holder should clearly specify which document is used as reference information for the authorised indications in the PSUR.

- Other options for the reference product information – When no CCDS or CCSI exist for a product (e.g. where the product is authorised in only one country or region, or for established/generics products on the market for many years), the marketing authorisation holder 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 authorised 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 (see VII.B.5.20.).

The marketing authorisation holder 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 section 4 (“Changes to the reference safety information”) and where relevant, discussed in PSUR section 16 (“Signal and risk evaluation”). These changes may include:

- changes to contraindications, warnings/precautions sections;
- addition to adverse reactions and interactions;
- addition of important new information on use in overdose; and
- removal of an indication or other restrictions for safety or lack of efficacy reasons.

The marketing authorisation holder 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) as an appendix to the PSUR (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 authorised product information (e.g. new adverse drug reaction, warning or contraindication) has been added to the reference safety information during the period from the data lock point to the submission of the PSUR, this information should be included in the PSUR section 14 (“Late-breaking information”), if feasible.

If stipulated by applicable regional requirements, the marketing authorisation holder should provide, in the regional appendix, information on any final, ongoing and proposed changes to the national or local authorised product information

VII.B.5. Format and contents of the PSUR

The PSUR 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. Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment.

Because clinical development of a medicinal product frequently continues following marketing authorisation, relevant information from post-authorisation studies or clinical trials in unauthorised indications or populations should also be included in the PSUR. 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 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 authorisation.

Examples of sources of efficacy, effectiveness and safety information that may be used in the preparation of PSURs include the following:

- non-clinical studies;
- spontaneous reports;
- active surveillance systems (e.g. sentinel sites);
- investigations of product quality;
- product usage data and drug utilisation information;
- clinical trials, including research in unauthorised indications or populations;
- observational studies, including registries;
- patient support programs;

- systematic reviews and meta-analysis;
- marketing authorisation holders sponsored websites²⁷;
- published scientific literature or abstracts, including information presented at scientific meetings;
- unpublished manuscripts made available to the marketing authorisation holder;
- licensing partners, other sponsors or academic institutions and research networks;
- competent authorities (worldwide) websites.

The above list is not intended to be all inclusive, and additional data sources may be used by the marketing authorisation holder to present safety, efficacy and effectiveness information in the PSUR and to evaluate the risk-benefit balance, as appropriate to the product and its known and emerging important benefits and risks. When desired by the marketing authorisation holder, a list of the sources of information used to prepare the PSUR can be provided as an appendix to the PSUR.

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 marketing authorisation holder 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 recognised 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 marketing authorisation holder. For example, for a marketing authorisation holder sponsored clinical trial, there should be access to patient level data while for a clinical trial not sponsored by the marketing authorisation holder, only the published report may be accessible .

When preparing the PSUR, 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

²⁷ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

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 signature⁴

- Part II: Executive Summary

- Part III: Table of Contents

1. Introduction

2. Worldwide marketing authorisation 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

- 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
- 15. Overview of signals: new, ongoing or closed
- 16. Signal and risk evaluation
 - 16.1. Summaries of safety concerns
 - 16.2. Signal evaluation
 - 16.3. Evaluation of risks and new information
 - 16.4. Characterisation of risks
 - 16.5. Effectiveness of risk minimisation (if applicable)
- 17. Benefit evaluation
 - 17.1. Important baseline efficacy and effectiveness information
 - 17.2. Newly identified information on efficacy and effectiveness

- 17.3. Characterisation of benefits
- 18. Integrated benefit-risk analysis for authorised indications
 - 18.1. Benefit-risk context – Medical need and important alternatives
 - 18.2. Benefit-risk analysis evaluation
- 19. Conclusions and actions
- 20. Appendices to the PSUR

PSUR title page

The title page should include the name of the medicinal product(s)⁵ and substance, international birth date, reporting interval, date of the report, marketing authorisation holder details and statement of confidentiality of the information included in the PSUR. The title page shall also contain the signature.

PSUR 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 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 authorised;

- summary of the overall benefit-risk analysis evaluation (based on sub-section 18.2 “benefit-risk analysis evaluation” of the PSUR);
- actions taken and proposed for safety reasons including significant changes to the investigator brochure and post-authorisation product information or other risk minimisation activities;
- conclusions.

PSUR table of contents

The executive summary should be followed by the table of contents.

VII.B.5.1. PSUR section “Introduction”

The marketing authorisation holder should briefly introduce the product(s) so that the PSUR “stands alone” but it is also placed in perspective relative to previous PSURs and circumstances. The introduction should contain the following information:

- International birth date (IBD), the date of the first marketing authorisation 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, authorised 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 section “Worldwide marketing authorisation status”

This section of the PSUR provides cumulative information and should contain a brief narrative overview including: date of the first authorisation worldwide, indications(s), authorised dose(s), and where authorised.

VII.B.5.3. PSUR section “Actions taken in the reporting interval for safety reasons”

This section of the PSUR 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 marketing authorisation holder, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:

- a significant influence on the risk-benefit balance of the authorised medicinal product; and/or
- an impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

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 summarised in this section.

Examples of significant actions taken for safety reasons include:

Actions related to investigational uses:

- refusal to authorise a clinical trial for ethical or safety reasons;
- partial or complete clinical trial suspension or early termination of an ongoing clinical trial because of safety findings or lack of efficacy;
- recall of investigational drug or comparator;
- failure to obtain marketing authorisation for a tested indication including voluntary withdrawal of a marketing authorisation application;
- risk management activities, including: – protocol modifications due to safety or efficacy concerns (e.g. dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
– restrictions in study population or indications;
– changes to the informed consent document relating to safety concerns;
– formulation changes;

- addition by regulators of a special safety-related reporting requirement;
- issuance of a communication to investigators or healthcare professionals; and
- plans for new studies to address safety concerns.

6“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 a marketing authorisation renewal;
- withdrawal or suspension of a marketing authorisation;
- actions taken due to product defects and quality issues;
- risk management activities including: – significant restrictions on distribution or introduction of other risk minimisation measures;
 - significant safety-related changes in labelling documents including restrictions on use or population treated;
 - communications to health care professionals; and
 - new post-marketing study requirement(s) imposed by competent authorities.

VII.B.5.4. PSUR section “Changes to reference safety information”

This PSUR 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 adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PSUR.

VII.B.5.5. PSUR section “Estimated exposure and use patterns”

PSURs 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 marketing authorisation holder, including the results of observational or drug utilisation studies.

This PSUR 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 PSURs for the same medicinal product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR introducing the change and any important difference between the results using the two methods should be highlighted.

VII.B.5.5.1. PSUR sub-section “Cumulative subject exposure in clinical trials”

This section of the PSUR should contain the following information on the patients studied in clinical trials sponsored by the marketing authorisation holder, 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 programme); it is recognised 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 randomised 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 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). Although it is recognised 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-authorisation (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-authorisation use in special populations:

Where post-authorisation 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:

- paediatric 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. Pattern of use of the medicinal product:

If the marketing authorisation holder 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 marketing authorisation holder may briefly comment on whether such use is supported by clinical guidelines, clinical trial evidence, or an absence of authorised 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 section “Data in summary tabulations”

The objective of this PSUR section is to present safety data through summary tabulations of serious adverse events from clinical trials, spontaneous serious and non-serious reactions from marketing experience (including reports from healthcare professionals, consumers, scientific literature, competent authorities (worldwide)) and serious reactions from non-interventional studies and other non-interventional solicited source. At the discretion of the marketing authorisation holder graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the preferred term (PT) level and system organ class (SOC) 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-E2A²⁸. 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 PSURs.

VII.B.5.6.1. PSUR sub-section “Reference information”

This sub-section of the PSUR should specify the version(s) of the coding dictionary used for presentation of adverse events/reactions.

VII.B.5.6.2. PSUR sub-section “Cumulative summary tabulations of serious adverse events from clinical trials”

This PSUR sub-section should provide background for the appendix that provides a cumulative summary tabulation of serious adverse events reported in the marketing authorisation holder’s clinical trials, from the DIBD to the data lock point of the current PSUR. The marketing authorisation holder 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 organised 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 programme. Data can be integrated across the programme. 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:

²⁸ ICH Topic E2A. Clinical safety data management: Definitions and standards for expedited reporting

- Causality assessment is generally useful for the evaluation of individual rare adverse drug reactions. Individual case causality assessment has less value in the analysis of aggregate data,

where group comparisons of rates are possible. Therefore, the summary tabulations 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 marketing authorisation holders should not unblind data for the specific purpose of preparing the PSUR.
- 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 sub-section “Cumulative and interval summary tabulations from post-marketing data sources”

This sub-section of the PSUR 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. 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 studies²⁹. 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 organised 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.

⁹ See footnote 8.

As described in ICH-E2D guideline³⁰, 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 sub-section.

An example of summary tabulations of adverse drug reactions from post-marketing data sources can be found in VII. Appendix 1 table VII.8.

²⁹ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

³⁰ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

VII.B.5.7. PSUR section “Summaries of significant findings from clinical trials during the reporting interval”

This PSUR 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 categorised by sex and age (particularly paediatrics versus adults), indication, dose, and region should be presented.

In addition, the marketing authorisation holder should include an appendix listing the sponsored interventional trials with the primary aim of identifying, characterising, 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 Section 15 (“Overview on signals: new, ongoing or closed”). For those that are considered to be either a potential or identified risk, the risk should be evaluated and characterised in PSUR Sections 16.2 (“Signal evaluation”) and 16.4 (“Characterisation of risks”), respectively.

VII.B.5.7.1. PSUR sub-section “Completed clinical trials”

This sub-section of the PSUR 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 sub-section “Ongoing clinical trials”

If the marketing authorisation holder is aware of clinically important information that has arisen from ongoing clinical trials (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this sub-section should briefly summarise 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 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 sub-section “Other therapeutic use of medicinal product”

This sub-section of the PSUR should include clinically important safety information from other programmes conducted by the marketing authorisation holder that follow a specific protocol, with solicited reporting as per ICH-E2D³¹ (e.g. expanded access programmes, compassionate use programmes, particular patient use, and other organised data collection).

VII.B.5.7.5. PSUR 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 PSURs is also authorised or under development as a component of a fixed combination product or a multi-drug regimen, this sub-section should summarise important safety findings from use of the combination therapy.
- If the product itself is a fixed combination product, this PSUR sub-section should summarise important safety information arising from the individual components whether authorised or under development.

The information specific to the combination can be incorporated into a separate section(s) of the PSUR for one or all of the individual components of the combination.

³¹ ICH-E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

VII.B.5.8. PSUR section “Findings from non-interventional studies”

This section should also summarise relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorisation holder-sponsored non-interventional studies that became available during the reporting interval (e.g. observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when relevant to multiple regions.

The marketing authorisation holder should include an appendix listing marketing authorisation holder-sponsored non-interventional studies conducted with the primary aim of identifying, characterising 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 (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. As for other information sources, the marketing authorisation holder should present signals or risks identified from such information in the relevant sections of the PSUR.

VII.B.5.9. PSUR section “Information for other clinical trials and Sources”

VII.B.5.9 1. PSUR sub-section “Other clinical trials”

This PSUR sub-section should summarise information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources which are accessible by the marketing authorisation holder during the reporting interval (e.g. results from pool analysis or meta-analysis of randomised clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

VII.B.5.9 2. PSUR sub-section “Medication errors”

This sub-section should summarise 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 section “Non-clinical data”

This PSUR section should summarise 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 authorised indications”) of the PSUR.

VII.B.5.11. PSUR section “Literature”

This PSUR 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 marketing authorisation holder became aware of during the reporting interval, when relevant to the medicinal product.

Literature searches for PSURs 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 paediatric 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 Convention³²
33 .

Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication [Updated April 2010] Publication Ethics: Sponsorship, Authorship, and Accountability, International Committee of Medical Journal Editors. http://www.icmje.org/urm_full.pdf

VII.B.5.12. PSUR section “Other periodic reports”

This PSUR section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSURs are prepared in agreement with the competent authority. In general, the marketing authorisation holder should prepare a single PSUR for a single active substance (unless otherwise specified by the SFDA); however if multiple PSURs are prepared for a single

³² Uniform requirements for manuscripts submitted to biomedical journals. International Committee of Medical Journal Editors. N Engl J Med. 1997 Jan 23;336(4):309-15. Available online: <http://www.nejm.org/doi/full/10.1056/NEJM199701233360422>

³³ ¹⁵Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication [Updated April 2010] Publication Ethics: Sponsorship, Authorship, and Accountability, International Committee of Medical Journal Editors. http://www.icmje.org/urm_full.pdf

medicinal product, this section should also summarise significant findings from other PSURs if they are not presented elsewhere within the report.

When available, based on the contractual agreements, the marketing authorisation holder should summarise 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 section “Lack of efficacy in controlled clinical trials”

This section should summarise 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 section “Late-breaking information”

The marketing authorisation holder should summarise in this PSUR 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. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the marketing authorisation holder, 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 (e.g. a well documented case of aplastic anaemia 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 (see VII.B.4.), where feasible.

The data presented in this section should also be taken into account in the evaluation of risks and new information (see VII.B.5.16.3.).

VII.B.5.15. PSUR section “Overview of signals: new, ongoing, or closed”

The general location for presentation of information on signals and risks within the PSUR is shown in figure VII.1 (see VII.B.5.21.). The purpose of this section is to provide a high level overview of signals³⁴ that were closed (i.e. evaluation was completed) during the reporting interval as well as ongoing signals that were undergoing evaluation at the end of the reporting interval. For the purposes of the PSUR, 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 marketing authorisation holder³⁵. 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 individual case safety report, case series) or quantitative (e.g. a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a competent authority (worldwide) (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.

³⁴ Signal” means information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action

³⁵ for the purpose of the PSUR, the term “signal” in this section corresponds with the term “validated signal” described in GVP Module IX.

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, this would also be considered a new signal on the basis that a new aspect of a previously refuted signal or recognised 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.

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 minimisation activities.

Within this section, or as an appendix the marketing authorisation holder should provide a tabulation of all signals ongoing or closed at the end of the reporting interval. This tabulation should include the following information:

- a brief description of the signal;
- date when the marketing authorisation holder became aware of the signal;

- status of the signal at the end of the reporting interval (close or ongoing);
- date when the signal was closed, if applicable;
- source of the signal;
- a brief summary of the key data;
- plans for further evaluation; and
- actions taken or planned.

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.

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 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, the marketing authorisation holder should summarise 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 section “Signal and risk evaluation”

These evaluation sub-sections should not unnecessarily duplicate information presented in previous sections of the PSUR but should rather provide interpretation and critical appraisal of the information, with a view towards characterising 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 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 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 summary³⁶ that is current at the start of the reporting interval of the PSUR. 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 health, (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-authorisation experience. Important identified and potential risks may include, for example:

- important adverse reactions;
- interactions with other medicinal products;
- interactions with foods and other substances;

³⁶ ICH-E2E – Pharmacovigilance planning

- medication errors;
- effects of occupational exposure; and
- pharmacological class effects.

The summary on important missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

VII.B.5.16.2. PSUR sub-section “Signal evaluation”

This sub-section of the PSUR should summarize the results of evaluations of all safety signals that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a 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 categorised 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 marketing authorisation holder.

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 categorised as important potential risks.
- Closed signals that are categorised as important identified risks.
- Closed signals that are potential risks not categorised as important.
- Closed signals that are identified risks not categorised 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 Standardised 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 sub-section “Evaluation of risks and new information”

This sub-section should provide a critical appraisal of new information relevant to previously recognised potential and identified risks, together with an update on important missing information. New information that constitutes a signal with respect to a previously recognised 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 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 categorised 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 characterisation of a previously recognised risk.

New information can be organised as follows:

1. New information on important potential risks.
2. New information on important identified risks.
3. New information on other potential risks not categorised as important.
4. New information on other identified risks not categorised 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. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated characterisation of important potential and identified risks in sub-section 16.4 (“Characterisation of risks”) of the report.

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 characterisation of any of the important potential and identified risks in sub-section 16.4 (“Characterisation 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 sub-section “Characterisation of risks”

This sub-section should characterise 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 characterisation of risk may include, where applicable:

- frequency;
- numbers of cases (numerator) and precision of estimate, taking into account the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk and precision of estimate;
- estimate of absolute risk and precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- patient characteristics relevant to risk (e.g., patient factors (age, pregnancy/lactation, hepatic/renal impairment, relevant co-morbidity, disease severity, genetic polymorphism);
- dose, route of administration;
- duration of treatment, risk period;

- preventability (i.e., predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker);
- reversibility;
- potential mechanism; and
- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

For PSURs 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 sub-section: “Effectiveness of risk minimisation (if applicable)”

Risk minimisation activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur. The aim of a risk minimisation activity is to reduce the probability or severity of an adverse drug reaction. Risk minimisation activities may consist of routine risk minimisation (e.g. product labelling) or additional risk minimisation activities (e.g. Direct Healthcare Professional Communication/educational materials).

The PSUR shall contain the results of assessments of the effectiveness of risk minimisation activities relevant to the risk-benefit assessment.

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this sub-section of the PSUR. Insights into the effectiveness of risk minimisation activities that may be applicable across multiple regions are of particular interest. Information may be summarised 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 regional appendix (see VII.B.5.20. and VII.C.5.6) to comply with national or regional requirements.

VII.B.5.17. PSUR section “Benefit evaluation”

VII.B.5.17.1. PSUR sub-section “Important baseline efficacy and effectiveness information”

This sub-section of the PSUR summarises information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval. This information should relate to authorised 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 characterised 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.

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

characterisation of the benefit of the medicinal product in PSUR sub-section 17.3 (“Characterisation of benefits”). 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 sub-section “Newly identified information on efficacy and effectiveness”

For some products, additional information on efficacy or effectiveness in authorised indications may have become available during the reporting interval. Such information should be presented in this sub-section of the PSUR. Substantive information on evidence supporting use in unauthorised indications should not be included unless relevant for the benefit-risk evaluation in the authorised 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 sub-section 17.1 (“Important baseline efficacy and effectiveness information”) if no new information became available.

VII.B.5.17.3. PSUR sub-section “Characterisation 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 authorised indications.

When there are no new relevant benefit data provided and no significant change in risk profile, this sub-section should refer to PSUR 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;
- generalisability 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 generalisable to patient populations treated in medical practice.

VII.B.5.18. PSUR section “Integrated benefit-risk analysis for authorised indications”

The marketing authorisation holder should provide in this PSUR 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 (“Characterisation 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 sub-section “Benefit-risk context - medical need and important alternatives”

This sub-section of the PSUR should provide a brief description of the medical need for the medicinal product in the authorised indications and summarised alternatives (medical, surgical or other; including no treatment).

VII.B.5.18.2. PSUR sub-section “Benefit-risk analysis evaluation”

A benefit-risk profile is generally specific to an indication and population. Therefore, for products authorised 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 authorised 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 generalisability, 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 unauthorised 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 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 section “Conclusions and actions”

A PSUR 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 authorised indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the marketing authorisation holder 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 optimise or further evaluate the risk-benefit balance for further discussion with the SFDA. This may include proposals for additional risk minimisation activities.

For products with a pharmacovigilance or risk management plan, the proposals should be incorporated into pharmacovigilance planning together with the risk minimisation plan (see Module V).

VII.B.5.20. Appendices to the PSUR

A PSUR 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.

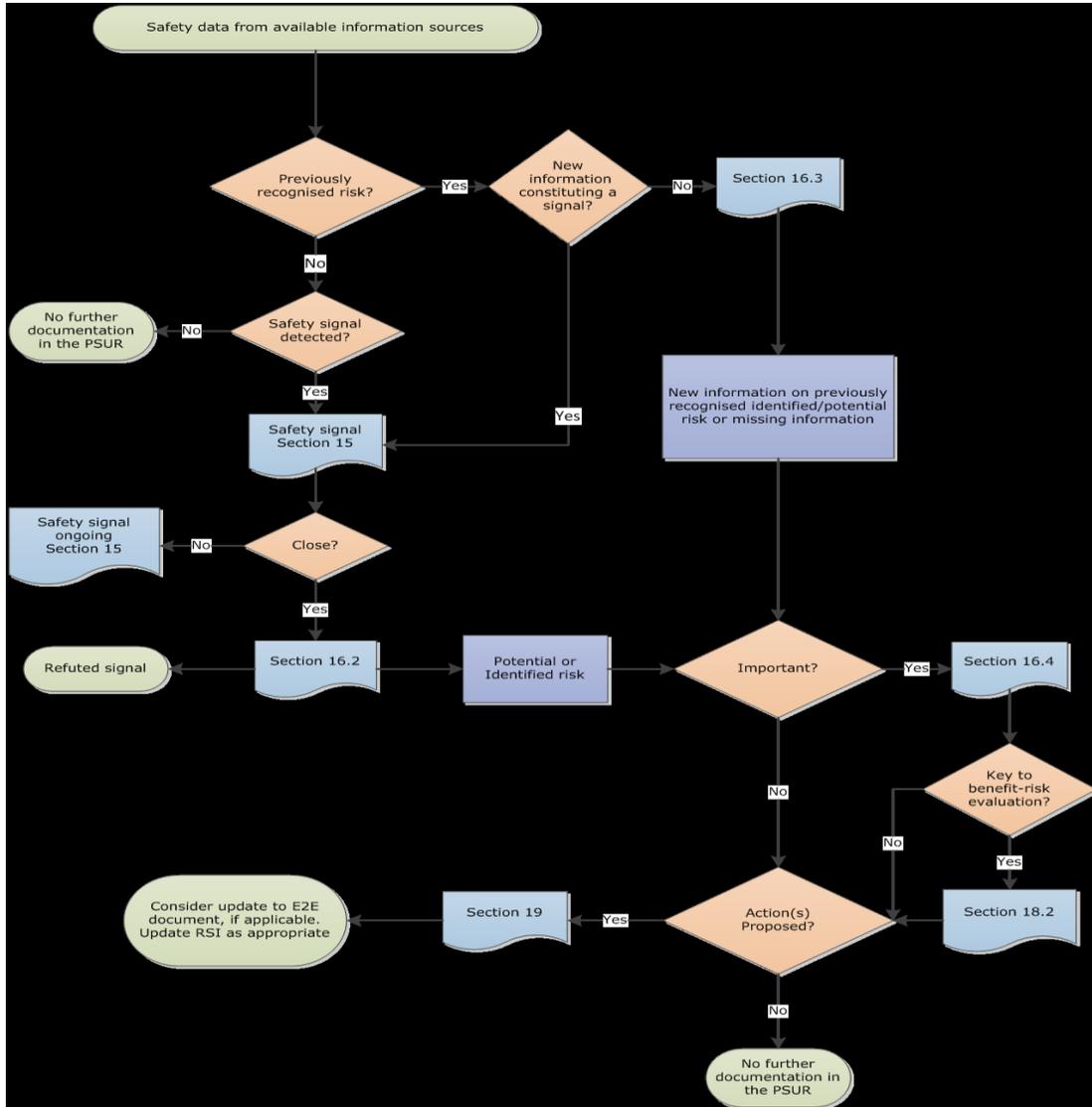
4. Tabular summary of safety signals.
5. Listing of all the marketing authorisation holder-sponsored interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product.
6. Listing of all marketing authorisation holder-sponsored non-interventional studies conducted with the primary aim of identifying, characterising 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 (when desired by the marketing authorisation holder).
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 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.

Figure VII.1. PSUR Sections/subsections – signals and risks.



VII.B.6. Quality systems for PSURs at the level of marketing authorisation holders

Marketing authorisation holders should have in place structures and processes for the preparation, quality control, review and submission of PSURs including follow-up during and after their assessment. These structures and processes should be described by means of written policies and procedures in the marketing authorisation holder’s quality system (see Module I).

There are a number of areas in the pharmacovigilance process that can directly impact the quality of PSURs, 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 PSURs. There should be documented procedures including quality control checks in place to check the accuracy and completeness of the data presented in the PSURs. 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 preparation. The PSUR should also contain the assessment of specific safety issues requested by competent authorities (worldwide). The marketing authorisation holder should have mechanisms in place to ensure that the requests made by competent authorities (worldwide) during the time of their PSUR 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 marketing authorisation holder's safety database to ensure accuracy of the number of events/reactions provided. The process for querying the safety database, the parameters used for the retrieval of the data and the quality control performed should be properly documented.

An appropriate quality system should be in place in order to avoid failure to comply with PSUR requirements such as:

- non-submission: complete non-submission of PSURs, 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 standardised medical terminology (e.g. MedDRA) and inappropriate dismissal of cases with no reported risk factors in cumulative reviews;
- submission of a PSUR where previous requests from competent authorities (worldwide) have not been addressed. Any significant deviation from the procedures relating to the preparation or submission of PSURs 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 is delegated to third parties, the marketing authorisation holder should ensure that they are subject to a quality system compliant with the current legislation. Explicit procedures and detailed agreements should exist between the marketing authorisation holder and third parties. The agreements may specifically detail the options to audit the PSUR preparation process.

VII.B.7. Training of staff members related to the PSUR process

For all organisations, 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 PSURs 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 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 process. Training records should demonstrate that the relevant training was delivered prior to performing PSUR-related activities.

VII.C. Operation within KSA

VII.C.1. Standard submission schedule of PSURs

Marketing authorisation holders shall submit PSURs according to the following submission schedule (hereafter “standard” submission schedule):

- at 6 months intervals once the product is authorised, even if it is not marketed;
- once a product is marketed, and based on the product international birth date , a 6 monthly PSUR 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.

VII.C.2. Application of the submission of PSURs

VII.C.2.1 Submission of PSURs for fixed dose combination products

If the substance that is the subject of the PSUR is also authorised as a component of a fixed combination medicinal product, the marketing authorisation holder shall either submit a separate PSUR for the combination of active substances authorised for the same marketing authorisation holder with cross-references to the single-substance PSUR(s), or provide the combination data within one of the single-substance PSURs.

VII.C.2.2. Submission of PSURs on demand of the SFDA

Marketing authorisation holders shall submit PSURs immediately upon request from the SFDA. When the timeline for submission has not been specified in the request, marketing authorisation holders should submit the PSUR within 90 calendar days of the data lock point.

VII.C.3. PSUR and risk management plan – common modules

The proposed modular formats for the PSUR and the RMP aim to address duplication and facilitate flexibility by enabling common PSUR/RMP sections to be utilised interchangeably across both reports. Common sections with the above mentioned reports are identified in Table VII.1.:

Common sections between RMP and PSUR (may not be in identical format)

RMP section	PSUR section
Part II, module SV – “Post-authorisation experience”, section “Regulatory and marketing authorisation holder action for safety reason”	Section 3 – “Actions taken in the reporting interval for safety reasons”
Part II, module SV – “Post-authorisation experience”, section “Non-study post-authorisation 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 – “Characterisation 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 reporting interval)	Sub-section 16.1 – “Summary of safety concerns”
Part V – “Risk minimisation measures”, section “Evaluation of the effectiveness of risk minimisation activities”	Sub-section 16.5 – “Effectiveness of risk minimisation (if applicable)”

VII.C.4. KSA specific requirements for periodic safety update reports

The scientific evaluation of the risk-benefit balance of the medicinal product included in the PSUR detailed in VII.B.5. shall be based on all available data, including data from clinical trials in unauthorised indications and populations.

Marketing authorization holders should submit below additional requirements:

- 1- Sub-section "KSA-approved product information":
This sub-section should contain 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. 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 minimisation activities based on PSUR 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: Adverse drug reactions 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

Marketing authorisation holders 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/randomisation 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
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	Other	US/Canada	Colombia	Japan	EU	Arab country concerned	Oral	Intravenous	Unknown	≥40	<40	Unknown	>65	>16 to 65	2 to ≤16	Female	Male
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

<u>System Organ Class</u> Preferred Term	Investigational medicinal product	Blinded	Active comparator	Placebo
<u>Blood and lymphatic system disorders</u>				
Anaemia				
Bone marrow necrosis				
<u>Cardiac disorders</u>				
Tachycardia				
Ischaemic cardiomyopathy				
<u><SOC></u>				

<PT>				
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Table VII.8. Numbers of adverse reactions by preferred term from post-authorisation 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>							
<PT>							
<PT>							
<SOC 2>							
<PT>							
<PT>							
<PT>							
<PT>							

* Non-interventional post-authorisation 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 trials)	Statistically significant increase in frequency	Review meta-analysis and available data	Pending
SJS	MMM/YYYY	Closed	MMM/YYYY	Spontaneous case reports	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 reports within 6 months of authorisation; 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 dermatologis t 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 marketing authorisation holder became aware of the signal.

Status:

Ongoing: Signal under evaluation at the data lock point of the PSUR. Anticipated completion date, if known, should be provided.

Closed: Signal for which evaluation was completed before the data lock point of the PSUR.

Note: A new signal of which the marketing authorisation holder 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.

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 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 Authorisation Number(s)	Date(s) of Authorisation	Marketing Authorisation Holder
<>	<>	<>	<>
<>	<>	<>	<>

INTERNATIONAL BIRTH DATE (IBD): <Date>

OTHER INFORMATION:

<Other identifying or clarifying information if necessary>

MARKETING AUTHORISATION HOLDER'S NAME AND ADDRESS:

<Name>

<Address>

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

NAME AND CONTACT DETAILS OF THE QPPV:

<Name>

<Address>

<Telephone number>

<Fax number>

<E-mail address>

SIGNATURE (QPPV or designated person): <Signature>

Annex 1

Format of periodic safety update reports

1. Electronic periodic safety update reports 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 periodic safety update reports

The periodic safety update report 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 authorisation 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. Characterisation of risks
 - 16.5. Effectiveness of risk minimisation (if applicable)
17. Benefit evaluation
 - 17.1. Important baseline efficacy and effectiveness information
 - 17.2. Newly identified information on efficacy and effectiveness
 - 17.3. Characterisation of benefits
18. Integrated benefit-risk analysis for authorised indications
 - 18.1. Benefit-risk context — Medical need and important alternatives
 - 18.2. Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices to the periodic safety update report

Module VIII – Post-authorisation Safety Studies

VIII.A. Introduction

A post-authorisation safety study (PASS) is defined as any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.

A PASS may be initiated, managed or financed by a marketing authorisation holder voluntarily, or pursuant to an obligation imposed by the SFDA.

This Module concerns PASS which are clinical trials or non-interventional studies and does not address non-clinical safety studies.

A PASS is non-interventional if the following requirements are cumulatively fulfilled:

- the medicinal product is prescribed in the usual manner in accordance with the terms of the marketing authorisation;
- 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.³⁷

The purposes of this Module are to:

- provide general guidance for the transparency, scientific standards and quality standards of non-interventional PASS conducted by marketing authorisation holders (VIII.B.);
- describe procedures whereby the SFDA may impose to a marketing authorisation holder an obligation to conduct a clinical trial or a non-interventional study (VIII.C.2.), and the impact of this obligation on the risk management system (VIII.C.3);
- describe procedures that apply to non-interventional PASS imposed as an obligation for the protocol oversight and reporting of results (VIII.C.4.) and for changes to the marketing authorisation following results (VIII.C.5.).

The guidance in VIII.B. applies to non-interventional PASS which are initiated, managed or financed by a marketing authorisation holder 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

³⁷[http://www.sfda.gov.sa/en/drug/drug_reg/Regulations/Clinical%20Trials%20Requirements%20Guidelines%20\(3\).pdf](http://www.sfda.gov.sa/en/drug/drug_reg/Regulations/Clinical%20Trials%20Requirements%20Guidelines%20(3).pdf)

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 apply to studies initiated, managed or financed by a marketing authorisation holder as well as those conducted by a third party on behalf of the marketing authorisation holder. This guidance applies to studies that involve primary collection of safety data directly from patients and health care professionals and those that make secondary use of data previously collected from persons and health care professionals for another purpose.

VIII.B.2. Terminology

Date at which a study commences: date of the start of data collection.

Start of data collection: the date from which information on the first study subject is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts. Simple counts in a database to support the development of the study protocol, for example to inform the sample size and statistical precision of the study, are not part of this definition.

End of data collection: the date from which the analytical dataset is completely available.

Analytical dataset: the minimum set of data required to perform the statistical analyses leading to the results for the primary objective(s) of the study.

Substantial amendment to the study protocol: amendment to the protocol likely to have an impact on the safety, physical or mental well-being of the study participants or that may affect the study results and their interpretation, such as changes to the primary or secondary objectives of the study, 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-authorisation 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 characterise 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 utilisation that add knowledge on the safety of the medicinal product (e.g. indication, dosage, co-medication, medication errors);
- to measure the effectiveness of a risk minimisation activity.

If the study fulfill the above mention objectives, the classification of a post-authorisation 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 marketing authorisation holders 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 the ENCePP Guide on Methodological Standards in Pharmacoepidemiology,³⁸ the ENCePP Checklist for Study Protocols², the Guideline on

³⁸ http://www.encepp.eu/standards_and_guidances/index.html

Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population for studies conducted in children,³⁹ and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP)⁴⁰.

For studies that are funded by a marketing authorisation holder, including studies developed, conducted or analysed fully or partially by investigators who are not employees of the marketing authorisation holder, the marketing authorisation holder should ensure that the investigators are qualified by education, training and experience to perform their tasks. The research contract between the marketing authorisation holder 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 marketing authorisation holder should consider the provisions of the ENCePP Code of Conduct⁴¹, and address the following aspects:

- rationale, main objectives and brief description of the intended methods of the research to be carried out by the investigator(s);
- rights and obligations of the investigator(s) and marketing authorisation holder;
- clear assignment of tasks and responsibilities;
- procedure for achieving agreement on the study protocol;
- provisions for meeting the marketing authorisation holder's pharmacovigilance obligations, including the reporting of adverse reactions and other safety data by investigators, where applicable;
- intellectual property rights arising from the study and access to study data;

³⁹ http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003764.pdf

⁴⁰ http://www.pharmacoepi.org/resources/guidelines_08027.cfm

⁴¹ http://www.encepp.eu/code_of_conduct/index.html

- storage and availability of analytical dataset and statistical programmes for audit and inspection;
- communication strategy for the scheduled progress and final reports;
- publication strategy of interim and final results.

Non-interventional post-authorisation 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 marketing authorisation holder and by third parties on behalf of the marketing authorisation holder.

Payments to healthcare professionals for participating shall be restricted to compensation for time and expenses incurred.

VIII.B.2. Study registration

Non International Post Aouthriazation Safety Study should be registered at the SFDA

VIII.B.3. Study protocol

All non-interventional post-authorisation safety studies 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 marketing authorisation holder may be required by the SFDA to submit the protocol. For PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.4 for the submission of the study protocol.

In order to ensure compliance of the marketing authorisation holder with its pharmacovigilance obligations, the qualified person responsible for pharmacovigilance

(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. **Marketing authorisation holder:** name and address of the marketing authorisation holder.

3. **Responsible parties:** names, titles, qualifications, addresses, and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators 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 programmes 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, categorise, analyse 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 programmes. 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, generalisability, 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-authorisation 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 marketing authorisation holder 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 marketing authorisation holder 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 individual case safety reports (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.

A statement should indicate if the study is a non-interventional post-authorisation study based on secondary use of data, for which the reporting of suspected adverse reactions in the form of individual case safety reports is not required (see GVP Module VI).

12. Plans for disseminating and communicating study results, including any plans for submission of progress reports and final reports.

13. References.

The format of the study protocol should follow the Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies published by the Agency⁴².

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.

⁴² http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf

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 risk-benefit balance of the product

The marketing authorisation holder shall monitor the data generated while the study is being conducted and consider their implications for the risk-benefit balance of the medicinal product concerned. Any new information that may affect the risk-benefit balance of the medicinal product should be communicated immediately in writing as an Emerging Safety Issue to the SFDA. Information affecting the risk-benefit 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 periodic safety update reports (PSURs) (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 marketing authorisation holder if appropriate) and reporting of suspected adverse reactions/adverse events should be put in place and summarised in the study protocol. If appropriate, reference can be made to the Pharmacovigilance System Master File (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 risk-benefit information arising from the study or the need for information about the study progress in the context of regulatory procedures or important safety communication about the product.

The timing of the 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 periodic safety update reports (PSURs) (see Module VII) and risk management plan (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.

For PASS initiated by the marketing authorisation holder pursuant to an obligation, see VIII.C.4 as regards submission of the final study report.

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. **Marketing authorisation holder:** name and address of the marketing authorisation holder.

4. **Investigators:** names, titles, degrees, addresses and affiliations of all main responsible parties, including the main author(s) of the protocol, the principal investigator, a coordinating investigator for each country in which the study is to be performed and other relevant study sites. A list of all collaborating institutions and investigators 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 analysed, 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 health care 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:

Key results: key results with reference to the study objectives, prior research in support of and conflicting with the findings of the completed post-authorisation safety study, and, where relevant, impact of the results on the risk-benefit balance of the product.

11.2. **Limitations:** limitations of the study taking into account circumstances that may have affected the quality or integrity of the data, limitations of the study approach and methods used to address them (e.g., response rates, missing or incomplete data, imputations applied), sources of potential bias and imprecision and validation of the events. Both direction and magnitude of potential biases 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. **Generalisability:** the generalisability (external validity) of the study results.

12. References.

13. **Other information:** any additional or complementary information on specific aspects not previously addressed.

The format of the final study report should follow the Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies published by the Agency⁴³.

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 risk-benefit balance of the product);
11. Marketing authorisation holder;
12. 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 marketing authorisation holder, the marketing authorisation holder 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

⁴³http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000199.jsp&mid=WC0b01ac05800250b3

ownership. The marketing authorisation holder 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 marketing authorisation holder 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

Marketing authorisation holders and investigators shall follow relevant national legislation and guidance of those Member States where the study is being conducted . The legislation on data protection must be followed.

For PASS imposed as an obligation, the marketing authorisation holder shall ensure that all study information is handled and stored so as to allow for accurate reporting, interpretation and verification of that information and shall ensure that the confidentiality of the records of the study subjects remains protected. This provision should be applied for all PASS.

VIII.B.7. Quality systems, audits and inspections

The marketing authorisation holder shall ensure the fulfilment of its pharmacovigilance obligations in relation to the study and that this can be audited, inspected and verified. For PASS imposed as an obligation, the marketing authorisation holder shall ensure that the analytical dataset and statistical programmes 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 (category 1 and 2 studies in GVP Module V) or required to investigate a safety concern of the RMP (category 3 of studies in Module V)

should be described in the RMP. All relevant sections/modules of the RMP should be amended to document the conduct of the study, including the safety specification, the pharmacovigilance plan, the risk minimisation plan and the summary of activities, as appropriate. Finalised protocols for studies in the pharmacovigilance plan should be provided in RMP annex 6 until submission of the final study report to the competent authorities. Studies looking at the effectiveness of risk minimisation measures should be included in the pharmacovigilance plan as well as described in detail in the risk minimisation plan. .

Other non-interventional PASS which are not obligations or required studies in the RMP but which could provide relevant information on the safety profile of the product (category 4 of studies in Module V) should be listed in the RMP section III “Summary table of additional pharmacovigilance activities.

VIII.C. Operation within the KSA

VIII.C.1. Procedure for imposing post-authorisation safety studies

The conduct of any post-authorisation safety study (PASS) can be imposed during the evaluation of the initial marketing authorisation application or during the post-authorisation phase by the SFDA whenever there are concerns about the risks of an authorised 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).

a. Request for a post-authorisation safety study as part of the initial marketing authorisation application

A marketing authorisation may be granted by the SFDA subject to the conduct of a PASS.

b. Request for a post-authorisation safety study during a post-authorisation regulatory procedure

The need for a PASS could be identified by the SFDA during a post-authorisation regulatory procedure, for example, an extension or a variation to a marketing authorisation or a renewal procedure.

c. Request for a post-authorisation safety study due to an emerging safety concern

After the granting of the marketing authorisation, the SFDA, may impose on the marketing authorisation holder an obligation to conduct a post-authorisation safety study if there are concerns about the risk of the authorised medicinal product,

d. Joint post-authorisation safety studies

If safety concerns apply to more than one medicinal product, the SFDA, encourage the marketing authorisation holders concerned to conduct a joint PASS. A joint PASS may also be necessary where there are limited patients (rare diseases) or the adverse reaction is rare. Requests to the marketing authorisation holders should contain the justification for the request of a joint study and may include core elements for the study protocol.. Upon request from the marketing authorisation holders, the SFDA may provide suggestions for a joint study 647 proposal and facilitate agreement in developing a joint protocol.

e. 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 authorisation, the marketing authorisation holder 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 marketing authorisation holder, the SFDA shall withdraw or confirm the obligation. When the obligation is confirmed, the marketing authorisation shall be subject to variation to include the obligation as a condition and the risk management plan (RMP), where applicable, shall be updated accordingly (see Module V).

VIII.C.2. Supervision of non-interventional post-authorisation safety studies conducted pursuant to an obligation

VIII.C.2.1. Roles and responsibilities of the marketing authorisation holder

The marketing authorisation holder 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 authorisation to conduct a non-interventional PASS, the marketing authorisation holder shall develop a study protocol and submit it to the SFDA for review.

The marketing authorisation holder has the responsibility to ensure that the study is not a clinical trial.

The marketing authorisation holder shall develop the study protocol following recommendations set out in VIII.B.5.1. The study may commence only when the written endorsement from the SDA, as appropriate, has been issued.

After a non-interventional imposed PASS has been commenced, the marketing authorisation holder shall submit any substantial amendments to the protocol, before their implementation, to the SFDA.

Upon completion of the study, the marketing authorisation holder 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

When the SFDA is involved in the oversight of the study, the SFDA will nominate rapporteur responsible for the supervision of the PASS. The SFDA rapporteur should write a protocol assessment report, including a list of questions if appropriate, and submit it for review and approval by the SFDA.

If the study proves to be interventional, the SFDA rapporteur should not provide an assessment report but should issue an explanatory statement to the marketing authorisation holder that the study is a clinical trial.

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 marketing authorisation holder 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 marketing authorisation holder of its endorsement or objection. The SFDA will provide the marketing authorisation holder 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 marketing authorisation holder should resubmit an amended version of the protocol.

VIII.C.3. Changes to the marketing authorisation following results from a non-interventional post-authorisation safety study

The marketing authorisation holder shall evaluate whether the study results have an impact on the marketing authorisation and shall, if necessary, submit to the SFDA. 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 authorisation. The recommendation by the SFDA shall mention any divergent positions and the grounds on which they are based.

VIII. Appendix 1. Methods for post-authorisation safety studies

VIII.App1.1. Study designs

Post-authorisation 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 organised 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 computerised 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,

haematological 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 haemodialysis centres. 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 computerised 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, 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. More detailed information on adverse events from a large number of physicians and/or patients may be collected.

VIII.App1.1.1.3. Registries

A registry is an organised 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 database.

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 utilisation 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 randomised 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 patients 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 standardised 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 authorised 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 programmes 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 is 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 aetiology fraction attributed to medicinal products, including blood dyscrasias or serious skin disorders.

VIII.App1.1.2.4. Other designs

Other 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, legalisation of the 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 metabolise 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 randomised 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 risk-benefit 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. Pragmatic trials are a kind of large simple trials.

VIII.App1.1.4. Drug utilisation studies

Drug utilisation 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 randomised 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-authorisation 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

Pharmacoepidemiological 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 pharmacoepidemiological studies or in their validation phase.

Marketing authorisation holders 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 taken into account. 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 marketing authorisation holder 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 Report of the Council for International Organisations of Medical Sciences Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance (CIOMS, Geneva 2010) defines a signal as *information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.*

For the purpose of this Module, only new information related to adverse effects will be considered.

In order to suggest a new potentially causal association or a new aspect of a known association, any signal should be validated taking into account other relevant sources of information.

The signal management process can be defined as the set of activities performed to determine whether, based on an examination of individual case safety reports (ICSRs), aggregated data from active surveillance systems or studies, literature information or other data sources, there are new risks associated with an active substance or a medicinal product or whether known risks have changed. The signal management process shall include all steps from initial signal detection; through their validation and confirmation; analysis and prioritisation; and signal assessment to recommending action, as well as the tracking of the steps taken and of any recommendations made.

The signal management process concerns all stakeholders involved in the safety monitoring of medicinal products including patients, healthcare professionals, marketing authorisation holders, regulatory authorities, scientific committees and decision-making bodies.

Whereas the National Pharmacovigilance and Drug Safety Center NPC database will be a major source of pharmacovigilance information, the signal management process covers signals arising from inside and outside the NPC database or not directly supported by the NPC database. For the purpose of monitoring data in NPC database, only signals related to an adverse reaction shall be considered.

In this Module, all applicable legal requirements are referenced as explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

The objectives of this Module are:

- to provide general guidance and requirements on structures and processes involved in signal management (section IX.B.);
- to describe how these structures and processes are applied in the setting of the pharmacovigilance and regulatory network (section IX.C.).

IX.B. Structures and processes

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, pharmacovigilance and pharmacoepidemiological data. Specific sources for signals include spontaneous adverse drug reaction (ADR) reporting systems, active surveillance systems, non-interventional studies, clinical trials, scientific literature and other sources of information.

Signals from spontaneous reports may be detected from monitoring of individual case safety reports (ICSRs), ADR databases, articles from the scientific literature or review of information provided by marketing authorisation holders in the context of regulatory procedures (e.g. variations, renewals, post-authorisation commitments, periodic safety update reports (PSURs), Risk Management Plan (RMP) updates or from other activities related to the on-going benefit-risk monitoring of medicinal products.

Spontaneous reports of ADRs may also be notified to poison centres, teratology information services, vaccine surveillance programmes, reporting systems established by marketing authorisation holders, and any other structured and organised data collection schemes allowing patients and healthcare professionals to report suspected adverse reactions related to medicinal products. The SFDA should liaise with other institutions or organisations managing such reporting system so as to be informed of these suspected adverse reactions.

Due to the increase in volume of spontaneous reports of (ADRs), the introduction of electronic safety reporting by patients and healthcare professionals and the mandatory electronic transmission of case reports from marketing authorisation holders to the SFDA, signal detection is now increasingly based on periodic monitoring of large databases.

Signals may arise from a wide range of different study types, including quality, non-clinical, interventional and non-interventional studies, systematic reviews and meta-analyses. Interventional trials and observational studies may, by design, recruit and follow-up a defined population of subjects who may experience ADRs. Review of aggregated data and statistical analyses may also point to an elevated risk of an adverse event to be further investigated as a signal.

Published results of relevant studies should be identified by marketing authorisation holders by screening the scientific literature. For general guidance on performing literature searches, refer to Module VI.

Marketing authorisation holders should regularly screen internet or digital media under their management or responsibility as specified in Module VI, for potential reports of suspected ADRs, which may characterise a new signal. Marketing authorisation holders and the SFDA should seek further information related to suspected ADRs they become aware of from any source. Suspected serious ADRs should be confirmed if possible through other data sources.

IX.B.2. Methodology for signal detection

As a general principle, signal detection should follow a recognised methodology, which may vary depending on the type of medicinal product it is intended to cover. Vaccines may for example require other methodological strategies.

The detection of signals shall be based on a multidisciplinary approach. Signal detection within the NPC database shall be complemented by statistical analysis where appropriate.

In order to determine the evidentiary value (i.e. the supporting evidence) of a signal a recognised methodology shall be applied taking into account the clinical relevance, quantitative strength of the association, the consistency of the data, the exposure-response relationship, the biological plausibility, experimental findings, possible analogies and the nature and quality of the data. Different factors may be taken into account for the prioritisation of signals, namely whether the association or the active substance/medicinal product is new, the strength of the association, the seriousness of the reaction involved and the documentation of the reports in the NPC database

IX.B.3. The signal management process

IX.B.3.1. Introduction

The signal management process covers all steps from detecting signals to recommending action(s) as follows:

- signal detection;
- signal validation;
- signal analysis and prioritisation;
- signal assessment;
- recommendation for action;
- exchange of information.

Although these steps generally follow a logical sequence, the wide range of sources of information available for signal detection may require some flexibility in the conduct of signal management e.g.:

- when signal detection is primarily based on a review of individual case safety reports (ICSRs), this activity may include validation and preliminary prioritisation of any detected signal;
- when a signal is detected from results of a study, it is generally not possible or practical to assess each individual case, and validation may require collection of additional data;
- recommendation for action (followed by decision in accordance with the applicable legislation) and exchange of information are components to be considered at every step of the process.

For the purpose of this guidance, signals originating from the monitoring of data from spontaneous reporting systems are considered as the starting point of the signal management process. The same principles should apply for data originating from other sources.

IX.B.3.2. Signal detection

Detailed guidance on methods of signal detection may be found in the Report of CIOMS Working group VIII Practical Aspects of Signal Detection in Pharmacovigilance.

Whichever methods are employed for the detection of signals, the same principles should apply, namely:

- the method used should be appropriate for the data set; for example, the use of complex statistical tools may not be appropriate for smaller data sets;
- data from all appropriate sources should be considered;
- systems should be in place to ensure the quality of the signal detection activity;
- any outputs from a review of cumulative data should be assessed by an appropriately qualified person in a timely manner;

- the process should be adequately documented, including the rationale for the method and periodicity of the signal detection activity.

Detection of signals may be performed based on a review of ICSRs, from statistical analyses in large databases, or from a combination of both.

IX.B.3.2.1. Review of individual case safety reports

As specified in Module VI, ICSRs may originate from a spontaneous reporting system, post-authorisation studies and monitoring of literature. Even a single report of a serious or severe adverse reaction (for example, one case of toxic epidermal necrolysis, aplastic anaemia or liver transplant) may be sufficient to raise a signal and to take further action. A review of ICSRs for this purpose should consider the number of cases (after exclusion of duplicates), the patient's demographics (including age and gender), the suspected medicinal product (including dose administered, formulation) and the suspected adverse reaction (including signs and symptoms), the temporal association, the clinical outcome in relation to drug continuation or discontinuation (i.e. de-challenge / re-challenge information). An assessment of causality of a suspected association should also consider, the presence of potential alternative causes including other concomitant medications, the underlying disease, the reporter's evaluation of causality and the plausibility of a biological and pharmacological relationship.

IX.B.3.2.2. Statistical analyses

Signal detection is now 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 defined active substances or medicinal products. Various methods have been developed to identify statistics of disproportionate reporting, i.e. higher reporting than expected for an suspected adverse reaction for an active substance/medicinal product of interest compared to all other active substances/medicinal products in the database, (expressed e.g. as a lower

bound of the proportionate reporting ratio >1). Given the limitations of these methods, 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.

Use of statistical tools may not be appropriate in all situations. The size of the data set, the completeness of the available information and the severity of the adverse reaction(s) should be taken into account when considering the use of statistical methods and the selection of criteria for the detection of signals.

The periodicity at which statistical reports should be generated and reviewed may vary according to the active substance/medicinal product, its indication and any known potential or identified risks. Some active substances/medicinal products may also be subject to an increased frequency of data monitoring (see IX.C.2.). The duration for this increased frequency of monitoring may also vary and be flexible with the accumulation of knowledge of the risk profile associated with the use of the concerned active substance/medicinal product.

IX.B.3.2.3. Combination of statistical methods and review of individual case safety reports

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 (IX.B.3.2.1.).

The statistical method should therefore be a supporting tool in the whole process of signal detection and subsequent validation.

IX.B.3.3. 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 demonstrating the existence of a new potentially causal association or a new aspect of a known association, and therefore justifies further analysis.

To validate a signal the following should be taken into account:

Clinical relevance including, for example:

– strength of evidence for a causal effect (e.g. number of reports, exposure, temporal

association, plausible mechanism, de/re-challenge, alternative explanation/confounders);

– 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:

– the extent to which information is already included in the SPC or PIL;

– whether the association has already been assessed in a PSUR or RMP, or was discussed at the level of a scientific committee or has been subject to a regulatory procedure.

In principle only a new signal for which there is no previous awareness should be validated. However, an already known association may give rise to a new signal if its apparent frequency of reporting, its duration, its severity or a change in the previously reported outcome (such as new fatality) suggests new information as compared with the information included in the SPC or previously assessed by the SFDA.

• 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.

The magnitude and clinical significance of a signal may also be examined by descriptive analyses in other available data sources or by analysis of the characteristics of exposed patients and their medicinal product utilisation patterns.

Signals for which the validity is not confirmed may deserve special attention in subsequent analyses i.e. it may be appropriate to continue to monitor the potential signal until there is enough evidence to confirm the signal. For example, there might be an inadequate case documentation or a supporting evidence of a causal association only in some of the ICSRs. In such scenarios, new cases of the same adverse reaction or follow-up reports of previously received cases should be reviewed at appropriate time intervals to ensure that all relevant cases are considered.

Marketing authorisation holders should establish tracking systems to capture the outcome of the validation of signals including the reasons why signals were not validated as well as information that would facilitate further retrieval of ICSRs and validation of signals.

IX.B.3.4. Signal analysis and prioritisation

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 in treated patients. These signals require urgent attention and need to be prioritised for further management without delay. This prioritisation process should consider:

- the impact on patients depending on the severity, reversibility, potential for prevention and clinical outcome of the association;
- the consequences of treatment discontinuation on the disease and the availability other therapeutic options;

- the strength and consistency of the evidence supporting an association, e.g., biological plausibility, a high number of cases reported in a short period of time, the measure of disproportionality of reporting and rapid increase of that measure over time and identification of the signal in different settings (e.g. general practice and hospital settings), data sources or countries;
- clinical context (e.g. whether the association suggest a clinical syndrome that may include other reactions);
- the public health impact, including the extent of utilisation of the product in the general population and in special populations (e.g. pregnant women, children or the elderly) and the patterns of medicinal product utilisation (e.g. off-label use or misuse). The public health impact may include an estimation of the number of patients that may be affected by an adverse reaction and this number could be considered in relation to the size of the general population, the population with the target disease and the treated population;
- increased frequency or severity of a known 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 a marketing authorisation application for a new active substance is still under evaluation.

In some circumstances, priority can also be given to signals identified for medicinal products or events with potential high media and pharmacovigilance stakeholder interest in order to communicate the result to the public and healthcare professionals as early as possible.

The outcome of signal prioritisation should include a recommendation of the time frame for the management of the signal.

The outcome of the signal prioritisation process should be entered in the tracking system, with the justification for the priority attributed.

IX.B.3.5. Signal assessment

The objective of signal assessment is to further evaluate a validated signal so as to identify the need for additional data collection or for any regulatory action. It consists of an assessment of the available pharmacological, non-clinical and clinical data and information from other sources. This review should be as complete as possible regarding the sources of information, including the application dossier, literature articles, spontaneous reports, expert consultation, and information held by marketing authorisation holders. When information is drawn from a range of sources, the strengths and limitations of each source should be considered in order to assess the contribution they can provide to the overall evaluation of the signal in terms of a recommendation for action. Summarising information from different data sources also requires the choice of an internationally agreed case definition (e.g. Brighton collaboration case definition for vaccines). If no such definition exists, an operational definition should be developed.

Signals may need to be assessed at a broader level e.g. at the therapeutic or system organ class level or at the level of a Standardised MedDRA⁴⁴ Query (i.e. SMQ). The search for information to assess the significance of a signal may also need to be extended to other products of the class and to 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), to a prior stage of a reaction (e.g. QT prolongation and torsades de pointes) or to clinical complications of the adverse reaction of interest (e.g. dehydration and acute renal failure).

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Gathering information from various sources may take time. For a new signal of a serious or severe adverse reaction, measures should be taken at any stage in the management of a signal including detection, if the information already available supports the conclusion that there is a potential risk that needs to be prevented or minimised in a timely manner.

⁴⁴ MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

IX.B.3.6. Recommendation for action

Signal assessment results in a recommendation that either no further action is required at this point in time or a further action is needed. Although the recommendation for action normally takes place in a logical sequence after signal assessment based on the extent of the information, the need for action should be considered throughout the signal management process. For example, the first case of an adverse reaction indicating a manufacturing defect may require immediate recall of a product batch. The review of available information at the signal validation or signal prioritisation stages may similarly conclude that the evidence is sufficiently strong to introduce temporary measures. In such situations, it is still necessary to proceed with a formal assessment of the signal to confirm or not the safety issue in order to extend or lift the temporary measures.

The recommendation for action may include a request for:

- immediate measures including the possibility of suspending the marketing authorisation of the medicinal product;
- additional information to be provided by the marketing authorisation holder, e.g. in order to confirm if a conclusion is valid for all indications and patient groups;
- periodic review of the signal, for example through PSURs (see Module VII);
- additional investigations or risk minimisation activities;
- an update of the product information through a regulatory procedure;
- conduct of a post-authorisation safety study (see Module VIII).

Whenever actions are requested of a marketing authorisation holder, the request should specify a timeframe by which they should be completed, including provision of progress reports and interim results, proportionate to the severity and public health impact of the signal.

IX.B.3.7. Exchange of information

Information on validated signals, Emerging Safety Issues and the outcome of signal assessments should be exchanged between the SFDA and marketing authorisation holders.

Marketing authorisation holders should communicate signals that may have implications for public health and the benefit-risk profile of a product immediately to the SFDA as an Emerging Safety Issue (see Module VI), and when appropriate this should include proposals for action.

The outcomes of signal assessment involving new or changed risks and risks that have an impact on the benefit-risk balance of the concerned active substance/medicinal products should be communicated to the public including health care professionals and patients (see IX.C.6.) as well as to the concerned marketing authorisation holders.

IX.B.4. Quality requirements

IX.B.4.1. Tracking

All validation, prioritisation, assessment, timelines, decisions, actions, plans, reporting as well as all other key steps should be recorded and tracked systematically. Tracking systems should be used for documentation and should also include signals, for which the validation process conducted was not suggestive of a new potentially causal association, or a new aspect of a known association. All records need to be archived (see Module I).

IX.B.4.2. Quality systems and documentation

An essential feature of a signal management system is that it is clearly documented to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are standardised, that these tasks are conducted by people with appropriate expertise and are clear to all parties involved and that there is provision for appropriate control and, when needed, improvement of the system. Therefore, a system of quality assurance and quality control consistent with the quality system standards should be in place and applied to all signal management processes (see Module I). Detailed procedures for this quality system should be developed, documented and implemented. The organisational roles and responsibilities for the activities and maintenance of documentation, quality control and review, and for ensuring corrective and preventive action need to be assigned and recorded. This should include the responsibilities for quality assurance auditing of the signal management system, including auditing of sub-contractors.

Data and document confidentiality (per the applicable regulations), security and validity (including integrity when transferred) should be guaranteed.

Through their tracking system, all parties should keep an audit trail of their signal management activities and of the relevant queries and their outcomes, including how signals have been detected, validated, confirmed and assessed.

Documentation may be requested from the marketing authorisation holders demonstrating compliance with these provisions and reviewed before and after marketing authorisation.

Staff should be specifically trained in signal management activities in accordance with their roles and responsibilities. The training system and location of the training records should be documented, and curricula vitae and job descriptions should be archived.

IX.C. Operation within the KSA

IX.C.1. Roles and responsibilities

The marketing authorisation holders and the SFDA should monitor data available in their database to determine whether there are new risks or whether risks have changed and whether those risks have an impact on the benefit-risk balance. A recognised signal detection methodology should be applied and detected signals should be validated, as appropriate.

IX.C.1.1. Roles and responsibilities of the SFDA

The SFDA shall specifically monitor data originated in the KSA, including data arising from sources mentioned in IX.B.1.

- shall monitor the data of the NPC database.
- shall validate and confirm any signal they have detected from NPC.
- shall confirm as soon as possible and no later than 30 days from its receipt any validated signal communicated by a marketing authorisation holder . In this context, where

the validity of the signal is not confirmed, special attention shall be paid to any follow-up information which may allow for the signal's confirmation, see IX.B.3.3.

The SFDA shall keep an audit trail of their signal detection activities

IX.C.1.2. Roles and responsibilities of marketing authorisation holder

The marketing authorisation holder should continuously monitor the safety of its medicinal products and inform the authorities of any changes that might have an impact on the marketing authorisation.

The marketing authorisation holder:

- shall monitor their database. The frequency of the monitoring should be at least once monthly and shall be proportionate to the identified risk, the potential risk and the need for additional information;
- shall validate any signal detected
- should notify in writing as an Emerging Safety Issue to the SFDA via email (NPC.Drug@sfda.gov.sa) (see also Module VI), any safety issue arising from its signal detection activity which could have a significant impact on the benefit-risk balance for a medicinal product and/or have implications for public health;
- should collaborate with the SFDA for the assessment of the signals by providing additional information upon request;
- should keep an audit trail of its signal detection activities.

IX.C.2. Periodicity of data monitoring in the NPC Database

The SFDA shall ensure the continuous monitoring of data in the NPC database with a frequency proportionate to the identified risk, the potential risk and the need for additional information. The monitoring should be based on a periodic review of statistical outputs (e.g. reaction monitoring reports) to determine whether there are new or changed risks in the safety profile of an active substance/medicinal product. The statistical outputs should contain ADRs in a structured hierarchy (e.g. MedDRA hierarchy) by active

substance(s)/medicinal product(s) and allow filters and thresholds to be applied on several fields as appropriate.

The baseline frequency for reviewing the statistical outputs from the NPC database should be once-monthly. The baseline frequency of data monitoring in the database may be increased if justified by the identified or potential risks of the product or by the need for additional information.

For products subject to additional monitoring (see Module X, which will be released), the frequency for reviewing the statistical outputs should be every 2 weeks until the end of additional monitoring. A 2-week frequency for reviewing the statistical outputs may also be applied for any other product taking into account the following criteria:

- any product considered to have an identified or potential risk that could impact significantly on the benefit-risk balance or have implications for public health. This may include risks associated with significant misuse, abuse or off-label use. The product may be moved back to baseline frequency of monitoring if risks are not confirmed;

- any product for which the safety information is limited due to low patient exposure during drug development, including products authorised under conditional approval or under exceptional circumstances, or for which there are vulnerable or poorly studied patient populations or important missing information (e.g. children, pregnant women, renal-impaired patients) while post-marketing exposure is likely to be significant;

- any product that contains active substances already authorised in the KSA but is indicated for use in a new patient population or with a new route of administration;

- any product for which the existing marketing authorisation has been significantly varied (e.g. changes to indication, posology, pharmaceutical form or route of administration), thereby modifying the exposed patient population or the safety profile.

Confirmation of a signal arising from the NPC data monitoring activities does not necessarily imply that the product has to be more frequently monitored and a risk proportionate approach should be applied.

More frequent monitoring than every 2 weeks should be based on a proposal from the SFDA. It should be targeted to a safety concern of interest especially during public health emergencies (e.g. pandemics).

IX.C.3. Processes for the SFDA regulatory follow-up

The SFDA may decide on any or a combination of the following actions:

- the marketing authorisation holder should conduct further evaluation of data and provide the results of that evaluation according to a defined timeline;
- the marketing authorisation holder should submit an *ad-hoc* PSUR;
- the marketing authorisation holder should sponsor a post-authorisation study according to an agreed protocol and submit the final results of that study;

- the marketing authorisation holder should be requested to submit a RMP or an updated RMP;
- the marketing authorisation holder should take any measures that are required for ensuring the safe and effective use of the medicinal product;
- the marketing authorisation should be varied, suspended, revoked or not renewed;
- urgent safety restrictions should be imposed;
- an inspection should take place in order to verify that the marketing authorisation holder for the medicinal product satisfies the pharmacovigilance requirements
- the medicinal product should be included in the list of medicinal products that are subject to additional monitoring within the scope.

Module XV – Safety communication

XV.A. Introduction

This Module provides guidance to marketing authorisation holders 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 summary of product characteristics (SPC), Patient Information Leaflet (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 take into account 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 as well as the guidance on communication planning given in Module XII, which will be realised.

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 provide 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 marketing authorisation holders and the SFDA in their preparation.

Throughout this Module, legal obligations are referred to as stated in the GVP Introductory Cover Note and are usually identified by the modal verb ‘shall’ (e.g. ‘the marketing authorisation holder shall...’). When guidance is provided on how to implement legal provisions, the modal verb ‘should’ is used.

XV.B. Structures and processes

XV.B.1. Objectives of safety communication

Safety communication aims at:

- providing timely, evidence-based information on the safe and effective use of medicines;
- facilitating changes to healthcare practices (including self-medication practices) where necessary;
- changing attitudes, decisions and behaviours in relation to the use of medicines;
- supporting risk minimisation behaviour;
- facilitating informed decisions on the rational use of medicines.

In addition to the above effective, high quality safety communication can support public confidence in the regulatory system.

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 (see Module XII, which will be realised).
- There should be adequate coordination and cooperation between the different parties involved in issuing safety communications (e.g. the SFDA, other public bodies and marketing authorisation holders).
- 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 realised).

- 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 marketing authorisation holders 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 organisations 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 marketing authorisation holders.

XV.B.4. Content of safety communication

Taking into account the principles in XV.B.2., safety communication should contain:

- important emerging information on any authorised 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 marketing authorisation holder and the SFDA on the safety information provided;
- information on any proposed change to the product information (e.g. the summary of product characteristics (SPC) or patient Information Leaflet (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 marketing authorisation holder 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 minimisation activities.

The preparation of DHPCs involves cooperation between the marketing authorisation holder and the SFDA. Agreement between these two parties should be reached before a DHPC is issued by the marketing authorisation holder. 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 realised).

Where there are several marketing authorisation holders of the same active substance for which a DHPC is to be issued, a single consistent message should normally be delivered. Whenever possible, it is advised that healthcare professionals' organisations 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 minimisation measure as part of a risk management plan (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 authorisation 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 minimise the potential risk).

The SFDA may disseminate or request the marketing authorisation holder 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 minimisation 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 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' organisations.

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 marketing authorisation holders. Their press releases may reflect the position of the marketing authorisation holder on a safety topic but should also make reference to any regulatory action taken by the SFDA. Relevant ongoing reviews should be mentioned in any communication by the marketing authorisation holder.

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 marketing authorisation holders 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 take into account 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 marketing authorisation holders should have systems in place for responding to enquiries about medicines from individual members of the public. Responses should take into account 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 minimisation measures often include specific programmes for risk communication. Tools used in such

programmes, 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 prioritising 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 behaviour, 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 marketing authorisation holder 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.B.8. Requirements for the marketing authorisation holder

As soon as a marketing authorisation holder 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 marketing authorisation holder shall be required to inform the SFDA.

XV.B.9. Consideration for third parties

Third parties (e.g. scientific journals, learned societies, patients' organisations) are encouraged to inform the SFDA of any relevant emerging information on the safety of medicines authorised 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 marketing authorisation holder shall ensure that information to the public is presented objectively and is not misleading.

Whenever a marketing authorisation holder becomes aware that a third party (e.g. scientific journals, learned societies, patients' organisations, professional societies) intends to issue communication that could potentially impact the benefit-risk balance of a medicinal product authorised in the KSA, the marketing authorisation holder should inform the SFDA and make every effort to share the content of the communications.

XV.B10. 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 marketing authorisation holders for the respective medicinal product(s) or active substance(s), either at the request of the SFDA, or on the marketing authorisation holder's own initiative. The marketing authorisation holder should seek the agreement of the SFDA regarding the content of a DHPC (and communication plan) prior to dissemination.

XV.C.10.1. 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.

The marketing authorisation holder should submit the following to the SFDA.

- **draft DHPC;**
- **the dissemination list** also known as “intended recipient list”: the intended recipients HCPs groups may be general practitioners, specialists, pharmacists, nurses; hospitals/ambulatory care/other institutions as appropriate. The list 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 centres, 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 centres, as well as the general public.
- **timetable for disseminating** the DHPC: the proposed timetable should be appropriate according to the urgency of the safety concern (usually maximum of 15 calendar days is considered appropriate);
- **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.

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 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.

After dissemination of a DHPC, a closing review should be performed by the MAH, a progress report may be submitted upon request of the SFDA.

In cases where a medicines authority in other country requests the dissemination of a DHPC in its territory, the marketing authorisation holder should notify the SFDA if this product is also authorized. This is in the context of the national legal requirement under which the marketing authorisation holder shall notify the SFDA of any new information which may impact the benefit-risk balance of a medicinal product.

XV.10.2. 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' organisations as appropriate.

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 marketing authorisation holder> 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 minimisation (e.g. contraindications, warnings, precautions of use) and, if applicable, switch to alternative treatment>
- <Recall information, if applicable, including level (pharmacy or patient) and date of recall>

<A statement indicating that the information is being sent in agreement with the national medicines authority, if applicable>

Further information on the safety concern and the recommendations

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, and, if known, the pharmacodynamic mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors), also the reason for disseminating the DHPC at this point in time>

<An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>

<A statement indicating any association between the adverse reaction and off-label use, if applicable>

<If applicable, details on the recommendations for risk minimisation>

<Placing of the risk in the context of the benefit>

<A statement on any previous DHPCs related to the current safety concern that have recently been distributed>

<A schedule for follow-up action(s) by the marketing authorisation holder/national medicines authority, if applicable>

Further information

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

<Therapeutic indication of the medicinal product, if not mentioned above>

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system>

<Mention if product is subject to additional monitoring and the reason why>

<Details (e.g. name, postal address, fax number, website address) on how to access the 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>

Module XVI– Risk Minimisation Measures: Selection of Tools and Effectiveness Indicators

XVI.A. Introduction

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

The guidance provided in this Module should be considered in the context of the wider GVP guidance, in particular in conjunction with Module V.

Risk minimisation measures may consist of routine risk minimisation or additional risk minimization measures. Routine risk minimisation is applicable to all medicinal products, and involves the use of the following tools, which are described in detail in Module V:

- the summary of product characteristics (SPC);
- the package leaflet;
- the labelling;
- the pack size and design;
- the legal (prescription) status of the product.

Safety concerns of a medicinal product are normally adequately addressed by routine risk minimization measures (see Module V). In exceptional cases however, routine risk minimisation measures will not be sufficient for some risks and additional risk minimisation measures will be necessary to manage the risk and/or improve the risk-benefit balance of a medicinal product. This module provides particular guidance on the use of additional risk minimisation measures, including the selection of tools and the evaluation of their effectiveness. In specific circumstances, however, the effectiveness evaluation may

also apply to routine risk minimisation measures associated with safety concern(s) which are described in the SPC/PIL (e.g. the SPC provides guidance for clinical actions beyond routine standards of clinical care for either the risk itself or management of the target population).

On the basis of the safety concerns described in the safety specification (see GVP Module V), the appropriate risk minimisation measures should be determined. Each safety concern needs to be individually considered and the selection of the most suitable risk minimisation measure should take into account the seriousness of the potential adverse reaction(s) and its severity (impact on patient), its preventability or the clinical actions required to mitigate the risk, the indication, the route of administration, the target population and the healthcare setting for the use of the product. A safety concern may be addressed using more than one risk minimisation measure, and a risk minimization measure may address more than one safety concern.

The marketing authorisation holder shall “monitor the outcome of risk minimisation measures which are contained in the risk management plan”.

This Module provides guidance on the principles for:

- The development and implementation of additional risk minimisation measures, including examples of risk minimisation tools;
- The evaluation of the effectiveness of risk minimisation measures.

Part XVI.B. describes the development, implementation and co-ordination of risk minimisation measures and the general principles of the evaluation of their effectiveness.

Part XVI.C. considers the application of those measures and principles in the setting of the KSA regulatory network.

In this Module, all applicable legal requirements are referenced in the way explained in the GVP Introductory Cover Note and are usually identifiable by the modal verb “shall”. Guidance for the implementation of legal requirements is provided using the modal verb “should”.

XVI.B. Structures and processes

XVI.B.1. General principles

Risk minimisation measures aim to optimise the safe and effective use of a medicinal product

throughout its life cycle. The risk-benefit balance of a medicinal product can be improved by reducing the burden of adverse reactions or by optimising benefit, through targeted patient selection and/or exclusion and through treatment management (e.g. specific dosing regimen, relevant testing, patient follow-up). Risk minimisation measures should therefore guide optimal use of a medicinal product in medical practice with the goal of supporting the provision of the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring.

The majority of safety concerns are addressed by routine risk minimisation measures (see Module V).

Exceptionally, for selected important risks, routine risk minimisation may be considered insufficient and additional risk minimisation measures may be deemed to be necessary. In determining if additional risk minimisation activities are needed, safety concerns should be prioritised in terms of frequency, seriousness, severity, impact on public health and preventability. Careful consideration should then be given to whether the goal can be reached with routine minimisation activities, and, if not considered feasible, which additional minimisation measure(s) is (are) the most appropriate. Additional risk minimisation measures should focus on the most important, preventable risks and the burden of imposing additional risk minimisation should be balanced with the benefit for patients.

A variety of tools are currently available for additional risk minimisation. This field is continuously developing, and new tools are likely to be developed in the future.

Technology advances, such as interactive web-based tools may gain prominence in the future in addition to the paper-based educational materials.

Successful implementation of additional risk minimisation measures requires contributions from all impacted stakeholders, including marketing authorisation applicants or holders, patients and healthcare professionals. The performance of these measures in healthcare systems requires assessment to ensure that their objectives are fulfilled and that the measures in place are proportionate taking account of the risk-benefit balance of the product and the efforts required of healthcare professionals and patients to implement the measures. It is therefore important to ensure that additional risk minimisation measures, including assessment of their effectiveness, do not introduce undue burden on the healthcare delivery system, the marketing authorisation holders, the regulators, and, most importantly, on the patients. To this aim, they should have a clearly defined objective relevant to the minimisation of specific risks and/or optimisation of the risk-benefit balance.

Clear objectives and defined measures of success with milestones need to guide the development of additional risk minimisation measures and close monitoring of both their implementation and ultimate effectiveness is necessary. The nature of the safety concern in the context of the risk-benefit balance of the product, the therapeutic need for the product, the target population and the required clinical actions for risk minimisation are factors to be considered when selecting risk minimisation tools and an implementation strategy to accomplish the desired public health outcome. The evaluation of effectiveness should facilitate early corrective actions if needed and may require modification overtime. It is recognised that this is an evolving area of medical sciences with no universally agreed standards and approaches. Therefore, it is important to take advantage of any relevant elements of methodology from pharmacoepidemiology and other disciplines, such as social/behavioural sciences and qualitative research methods.

The introduction of additional risk minimisation should be considered as a “programme” where specific tools, together with an implementation scheme and evaluation strategy are

developed. The description of risk minimisation measures, an integral part of the RMP (see Module V), should therefore give appropriate consideration to the following points:

□□Rationale: When additional risk minimisation measure(s) are introduced a rationale should be provided for those additional measures;

□□Objectives: Each proposed additional risk minimisation measure(s) should include defined

objective(s) and a clear description of how and which safety concern is addressed with the proposed additional risk minimisation measure(s);

□□Description: This section of the RMP should describe the selected additional risk minimisation

measures, including tools that will be used and key elements of content;

□□Implementation: This section of the RMP should provide a detailed proposal for the implementation of additional risk minimisation measures (e.g. setting and timing or frequency of intervention, details of the target audience, plan for the distribution of educational tools; how the action will be coordinated where more than one marketing authorisation holder is involved);

□□Evaluation: This section of the RMP should provide a detailed plan with milestones for evaluating the effectiveness of additional risk minimisation measures in process terms and in terms of overall health outcome measures (e.g. reduction of risk).

XVI.B.2.Risk minimisation measures

Risk minimisation measures aim to facilitate informed decision making to support risk minimization when prescribing, supplying and/or using a medicinal product. While routine measures are applied to every medicinal product (see details in Module V) additional risk minimisation activities should only be introduced when they are deemed to be essential for

the safe and effective use of the medicinal product and should be developed and provided by suitably qualified people.

Additional risk minimisation measures may differ widely in purpose, design, target audience and complexity. These measures might be used to guide appropriate patient selection with the exclusion of patients where use is contraindicated, to support on-treatment monitoring relevant to important risks and/or management of an adverse reaction once detected. Additionally, specific measures may be developed to minimise the risk of medication error and/or to ensure appropriate administration of the product where it is not feasible to achieve this through the product information and labelling alone.

Section XVI.B.2. describes additional risk minimisation measures that may be considered in addition to the routine measures, including:

- Educational programmes;
- Controlled access programmes;
- Other risk minimisation measures.

XVI.B.2.1. Educational programme

Educational programmes are based on targeted communication with the aim to supplement the information in the summary product characteristics (SPC) and package leaflet. Any educational material should focus on actionable goals and should provide clear and concise messages describing actions to be taken in order to prevent and minimised selected safety concerns.

The aim of an educational programme is to improve the use of a medicine by positively influencing the actions of healthcare professionals and patients towards minimising risk. Educational materials should therefore be built on the premise that there is an actionable recommendation for targeted education and that applying this measure is considered essential for minimising an important risk and/or for optimisation of the risk-benefit balance. In the context of an educational programme, the tools can have several different

target audiences, can address more than one safety concern and can be delivered using a combination of tools and media (e.g. paper, audio, video, web, in-person training).

Ideally, educational materials should be available in a range of formats so as to ensure that access is not limited by disability or access to the internet. When feasible the appropriateness of the tool and media for the target audience (e.g. suitable language, pictures, diagrammes, or other graphical support) should be user tested in advance, in order to optimise the success of the implementation phase. The content of any educational material should be fully aligned with the currently approved product information for a medicinal product, such as the SPC and package leaflet, and should add rather than duplicate SPC and package leaflet information. Promotional elements, either direct or veiled (e.g. logos, product brand colours, suggestive images and pictures), should not be included and the focus of the educational material should be on the risk(s) related to the product and the management of those risk(s) requiring additional risk minimisation.

Any educational programme should be completely separated from promotional activities and contact information of physicians or patients gathered through educational programmes should not be used for promotional activities.

The educational tools described below can be considered individually or in combinations while developing an educational programme for the purpose of additional risk minimisation.

XVI.B.2.1.1. Educational tools

An educational tool should have a clearly defined scope and should include unambiguous statement(s) regarding the important risk(s) of concern to be addressed with the proposed tool, the nature of such risk(s) and the specific steps to be taken by healthcare professionals and/or patients in order to minimise those risks. This information should focus on clearly defined actions related to specific safety concerns described in the RMP and should not be unnecessarily diluted by including information that is not immediately relevant to the

safety concern and that is adequately presented in the SPC or package leaflet. Educational tools should refer the reader to the SPC and the package leaflet. In addition to an introductory statement that the educational material is essential to ensure the safe and effective use and appropriately manage important selected risks, elements for inclusion in an educational tool could provide:

- guidance on prescribing, including patient selection, testing and monitoring;
- guidance on the management of such risks (to healthcare professionals and patients or carers);
- guidance on how and where to report adverse reaction of special interest.

Further guidance on the responsibilities of the applicant or marketing authorisation holder and the SFDA is provided in XVI.C.1. of this Module.

XVI.B.2.1.1.1 Educational tools targeting healthcare professionals

The aim of any educational tool targeting a healthcare professional should be to deliver specific recommendation(s) on the use (what to do) and/or contraindication(s) (what not to do) and/or warnings (how to manage adverse reactions) associated with the medicine and the specific important risks needing additional risk minimisation measures, including:

- selection of patients;
- treatment management such as dosage, testing and monitoring;
- special administration procedures, or the dispensing of a medicinal product;
- details of information which needs to be given to patients.

The format of a particular tool will depend upon the message to be delivered. For example, where a number of actions are needed before writing a prescription for an individual patient, a checklist may be the most suitable format. A brochure may be more appropriate to enhance awareness of specific important risks with a focus on the early recognition and management of adverse reactions, while posters for display in certain clinical environments

can include helpful treatment or dosage reference guides. Other formats may be preferable, depending on the scope of the tool.

XVI.B.2.1.1.2. Educational tools targeting patients and/or carers

The aim of tools targeting patients should be to enhance the awareness of patients or their carers on the early signs and symptoms of specific adverse reactions causing the need for additional risk minimisation measures and on the best course of action to be taken should any of those symptoms occur. If appropriate, a patient's educational tool could be used to provide information on the correct administration of the product and to remind the patient about an important activity, for example a diary for posology or diagnostic procedures that need to be carried out and recorded by the patient and eventually discussed with healthcare professionals, to ensure that any steps required for the effective use of the product are adhered to.

Patient alert card

The aim of this tool should be to ensure that special information regarding the patient's current therapy and its important risks (e.g. potential life-threatening interactions with other therapies) is held by the patient at all times and reaches the relevant healthcare professional as appropriate. The information should be kept to the minimum necessary to convey the key minimisation message(s) and the required mitigating action, in any circumstances, including emergency. Ability to carry with ease (e.g. can be fitted in a wallet) should be a key feature of this tool.

XVI.B.2.2 Controlled access programme

A controlled access programme consists of interventions seeking to control access to a medicinal product beyond the level of control ensured by routine risk minimisation measures i.e. legal status.

Since a controlled access programme has large implications for all stakeholders, the use of such a programme should be limited and should be guided by a clear therapeutic need for the product based on its demonstrated benefit (e.g. it treats a serious disease without

alternative therapies; it treats patients who have failed on existing therapies), the nature of the associated risk (e.g. risk is lifethreatening), and whether this risk is expected to be managed by the interventions. Therefore, controlled access should only be considered as a tool for minimising an important risk with significant public health or individual patient impact for a product with clearly demonstrated benefits but which would not otherwise be available without a programme where patient access is contingent on fulfilling one or more requirements prior to a product being prescribed or dispensed in order to assure its safe use.

Examples of requirements that need to be fulfilled before the product is prescribed and/or dispensed and/or used in a controlled access programme are listed below (they may be included individually or in combination):

- Specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria;
- Prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk of the product;
- Explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g. patient registry;
- Medicines made available for dispensing only to Pharmacies which are registered and approved to dispense the product.

On occasions, a requirement to test or to monitor a patient in a specific way can also be used as a controlled access tool. For example, monitoring of the patient's health status, laboratory values or other characteristic (e.g. an ECG) prior to and/or during treatment, e.g. liver function tests, regular blood tests, pregnancy test (which can be part of a pregnancy prevention programme). Measures should be put in place to ensure that monitoring takes place according to the SPC where this is critical to risk-benefit balance of the product.

XVI.B.2.3. Other risk minimisation measures

XVI.B.2.3.1 Controlled distribution systems

A controlled distribution system refers to the set of measures implemented to ensure that the stages of the distribution chain of a medicinal product are tracked up to the prescription

and/or pharmacy dispensing the product. Orders and shipments of product from a single or multiple identified distribution points in the KSA facilitate traceability of the product. For instance, this sort of measures could be considered for those products controlled in KSA under the respective national legislations about the misuse and abuse of medicines.

XVI.B.2.3.2 Pregnancy prevention programme

A pregnancy prevention programme (PPP) is a set of interventions aiming to minimise pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects. The scope of such a programme is to ensure that female patients are not pregnant when starting therapy or do not become pregnant during the course and/or soon after stopping the therapy. It could also target male patients when use of a medicinal product by the biological father might have a negative effect on pregnancy outcome.

A PPP combines the use of educational tools with interventions to control appropriately access to the medicine. Therefore, the following elements should be considered individually and/or in combination in the development of a PPP:

- Educational tools targeting healthcare professionals and patients to inform on the teratogenic risk and required actions to minimise this risk e.g. guidance on the need to use more than one method of contraception and guidance on different types of contraceptives; information included for the patient on how long to avoid pregnancy after treatment is stopped; information for when the male partner is treated;
- Controlled access at prescribing or dispensing level to ensure that a pregnancy test is carried out and negative results are verified by the healthcare professional before prescription or dispensing of the medicinal product (and);
- Prescription limited to a maximum of 30 days supply;
- Counselling in the event of inadvertent pregnancy and evaluation of the outcome of any accidental pregnancy.
- Consent form

The design and implementation of a pregnancy registry (as a stand-alone activity or as part of a pregnancy prevention programme) should also be considered for universal enrolment of patients who become pregnant during treatment or within an appropriate time from the

end of treatment e.g. 3 months. Use of this systematic tool to collect pregnancy outcome information can be helpful in assessing the effectiveness of the pregnancy prevention program and/or in facilitating further characterisation of the risk, particularly in the early period post authorisation when human pregnancy data may be very limited and/or when the potential concern may be based on non-clinical data alone.

XVI.B.2.3.3 Direct health care professional communication (DHPC)

A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by the SFDA, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. For example, a DHPC may aim at adapting prescribing behaviour to minimise particular risks and/or to reduce the burden of adverse reactions with a medicinal product. Situations where dissemination of a DHPC should be considered are detailed in Module XV.

XVI.B.3. Implementation of risk minimisation measures

When the risk management measures are approved, a distribution list should be sent to the National pharmacovigilance and Drug Safety Center in order to grant the approval for the distribution process.

Additional risk minimisation measures can consist of one or more interventions that should be implemented in a sustainable way in a defined target group. Careful consideration should be given to both the timing and frequency of any intervention and the procedures to reach the target population.

For example, a one-off distribution of educational tools may be insufficient to ensure that all potential prescribers and/or users, including new prescribers and users, are reached. Additional periodic redistribution of the tools might be necessary. Conversely, educational materials required at the time of launch of a new medicinal product may no longer be necessary or relevant once it has been available for a number of years. Because risk

minimisation measures serve different purposes, some measures such as alert cards, controlled access programmes and pregnancy prevention programmes, will usually apply to all future applications for the same medicinal product, whilst others, such as DHPCs and training materials, may not necessarily be needed for all future applications. The appropriateness of each measure and whether these will be required for the future applications for the same medicinal products should be carefully considered at the time of authorisation of the product (and made clear in the RMP). Careful consideration should be given to the layout and content of the educational tools to ensure a clear distinction from any promotional material distributed. Submission of educational material for review by the national the SFDA should be separate from submission of promotional material and a covering letter should clearly state whether the materials are promotional or educational. Furthermore, educational tools should be distributed separately from promotional materials as a 'stand-alone' communication and it should be clearly stated that the tools are not promotional material, but rather have risk minimisation purposes. Quality assurance mechanisms should ensure that the distribution systems in place are fit for purpose and auditable.

XVI.B.4. Effectiveness of risk minimisation measures

When the MAH grant the approval to start the distribution process, a report of the distribution process might be requested to be submitted periodically. Evaluating the effectiveness of additional risk minimisation measures is necessary to establish whether an intervention has been effective or not, and if not why not and which corrective actions are necessary. The evaluation should be performed for the additional risk minimisation tools individually and for the risk minimisation programme as a whole.

Effectiveness evaluation should be conducted at the most appropriate time, accounting for time required for launch of interventions, estimated use of the product into the healthcare system and other relevant circumstances.

Periodic review of the effectiveness of one or more specific tools or the overall programme, as appropriate should be also planned. Time points of particular relevance are as follows:

- after initial implementation of a risk minimisation programme (e.g. within 12-18 months), in order to allow the possibility of amendments, should they be necessary;
- in time for the evaluation of the renewal of a marketing authorisation; and whenever effectiveness is evaluated, careful consideration should be given on the need for continuing with the additional risk minimisation measure.

Effectiveness evaluation should address different aspects of the risk minimisation, the process itself (i.e. to what extent the programme has been implemented as planned), its impact on knowledge and behavioral changes in the target audience (i.e. the measure(s) in affecting behavioural change), and the outcome (i.e. to what extent the predefined objectives of risk minimisation were met, in the short and long term). In designing an evaluation strategy, due consideration needs to be made toward what aspects of process and outcomes can be realistically measured in order to avoid the generation of inaccurate or misleading data or placing an undue burden on the healthcare system or other stakeholders. The time of assessing each aspect of the intervention as well as setting of realistic metrics on which the effectiveness of the tool is judged, should also be carefully considered and planned prior to initiation.

To evaluate the effectiveness of additional risk minimisation measures two categories of indicators should be considered:

- Process indicators;
- Outcome indicators.

Process indicators are necessary to gather evidence that the implementing steps of additional risk minimisation measures have been successful. These process indicators should provide insight into what extent the programme has been executed as planned and whether the intended impacts on behavior have been observed. Implementation metrics should be identified in advance and tracked over time.

The knowledge gained may be used to support corrective implementation action as needed. Assessing the implementation process can also improve understanding of the process(es) and causal mechanism(s) whereby the additional risk minimisation measure(s) did or did not lead, to the desired control of specified important risks.

Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimisation measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.

In rare circumstances when it is fully justified that the assessment of outcomes indicators is unfeasible (e.g. inadequate number of exposed patients, very rare adverse events), the effectiveness evaluation may be based exclusively on the careful interpretation of data on process indicators.

The conclusion of the evaluation may be that risk minimisation should remain unchanged or modifications are to be made to existing activities. Alternatively, the assessment could indicate that risk minimisation is insufficient and should be strengthened (e.g. through amendment of warnings or recommendations in the SPC or package leaflet, improving the clarity of the risk minimisation advice and/or by adding additional tools or improving existing tools). Another decision may be that the risk minimisation is disproportionate or lacking a clear focus and could be reduced or simplified (e.g. by decreasing the number of tools or frequency of intervention, or by eliminating interventions proved to be non-contributory to risk minimisation). In all circumstances, the burden on the patient and the healthcare system should be given careful consideration.

In addition to assessing the effectiveness of risk minimisation measures in managing safety concerns, it is also important to monitor if the risk minimisation intervention may have had unintended (negative) consequences relevant to the public health question under consideration, either in the short and/or long term. Examples of unintended consequences may include undue burden on the healthcare system, or discontinuation of a product even if its risk-benefit balance remains positive.

if a study is conducted to assess behavioural or safety outcome indicators the detailed guidance for conducting a post-authorisation safety study, which is provided in Module VIII, should be followed. Such guidance does not apply to the measurement of simple process markers (e.g. distribution of the tools reaching the target population). The ENCePP

Guide on Methodological Standards in Pharmacoepidemiology⁴⁵ should be considered as appropriate.

XVI.B.4.1. Process indicators

Process indicators are measures of the extent of implementation of the original plan, and/or variations in its delivery. Process indicators should complement but not replace the assessment of the attainment of the objectives of the risk minimisation measures (i.e. outcome indicators). Depending on the nature of the interventions various process indicators can be identified for the assessment of their performance.

XVI.B.4.1.1 Reaching the target population

When risk minimisation measures involve the provision of information and guidance to healthcare professionals and/or patients by mean of educational tools, measures of distribution should be used to acquire basic information on implementation. These metrics should focus on assessing whether the materials were delivered to the target audience and whether they were actually received by the target population.

XVI.B.4.1.2 Assessing clinical knowledge

In order to assess the awareness of the target audience and the level of knowledge achieved by educational interventions and/or information provision (for example via an educational programme with a goal of preventing drug exposure during pregnancy), scientifically rigorous survey methods should be applied. Appendix I summarises key methodological aspects to be considered for the design and implementation of a survey.

A survey generally includes a core of standard questions administered through telephone contact, in person interview, or self-administered through postal/electronic

⁴⁵ <http://www.encepp.eu>

communication, which are repeated over time. Such an approach may be tailored to the monitoring of attitude and knowledge in a diverse sample, that includes representatives from each segment of interest in the target populations of healthcare professionals and/or patients. Psychometric measures should be used as appropriate.

Whenever feasible a randomised sample and an adequate sample size should be selected. In contrast, use of advocacy groups or patient support groups to survey knowledge can be considered to be inherently biased through self-selection, and should be avoided.

Appropriate attention should be given to the research objectives, study design, sample size and representativeness, operational definition of dependent and independent variables, and statistical analysis. Thorough consideration should also be given to the choice of the most appropriate data collection instruments (e.g. questionnaires).

XVI.B.4.1.3 Assessing clinical actions

In order to evaluate the effectiveness of educational interventions and/or information provisions, not only clinical knowledge but also the resulting clinical actions (i.e. prescribing behaviour) should be measured. Drug utilisation studies by means of secondary use of electronic records or through medical chart abstraction are valuable options to quantify clinical actions, if representative of the target population and where adequate databases are accessible. The analysis of prescription records, especially when linked to other records of patients (e.g. clinical and demographic data), may allow the evaluation of prescribing behaviour, including co-prescribing of two interacting medicinal products, compliance with laboratory monitoring recommendations, as well as patient selection and monitoring.

By applying appropriate statistical methods (e.g. time series analyses, survival analyses, logistic regression) to a cohort of medicines users, different aspects of prescribing or use may be assessed, which can provide insights beyond purely descriptive evidence.

The study of behaviour based on data collected through surveys should only be considered when no pre-existing data are available to evaluate clinical actions (i.e. conduct a drug

utilisation study based on self-reported data collected in healthcare professionals and/or patients survey).

XVI.B.4.2. Outcome indicators

The ultimate measures of success of a risk minimisation programme are the safety outcomes, i.e. the frequency and/or severity of adverse reactions in relation to patients' exposure to the medicine outside of an interventional study setting (i.e. non-interventional setting) and those safety outcomes should be the outcome indicator(s). Such an evaluation should involve the comparison of epidemiologic measures of outcome frequency such as incidence rate or cumulative incidence of an adverse reaction, obtained for example in the context of post-authorisation safety studies. The use of appropriate safety related outcomes of interest should be considered (e.g. a surrogate endpoint such as an adequate biomarker as a substitute for a clinical endpoint) if such an approach facilitates the effectiveness evaluation. Under any approach, scientific rigour and recognised principles of epidemiologic research should always guide the assessment of the final outcome indicator of interest. Comparisons of frequency before and after the implementation of the risk minimisation measures (i.e. pre-post design) should be considered. When a pre-post design is unfeasible (e.g. risk minimisation measures are put in place at the time of initial marketing authorisation), the comparison of an outcome frequency indicator obtained post-intervention against a predefined reference value obtained from literature review, historical data, expected frequency in general population, would be acceptable (i.e. observed versus expected analysis) and should take into account any stimulated reporting, changes in patient care and/or risk minimisation measures over time. The selection of any particular reference group should be appropriately justified. Methods to measure the effectiveness of risk minimisation measure should be proportionate to the risks being minimised. As such use of spontaneous reporting rates (i.e. number of suspected adverse reaction reports over a fixed time period) may be acceptable in the context of routine risk minimisation.

Spontaneous reporting should be considered with caution when estimating the frequency of adverse events in the treated population, but it may be used in very specific

circumstances, for instance when the adverse reaction with the product is rare and there is a negligible background incidence of the adverse event in the general population and a strong association between treatment and the adverse event. In those circumstances when a direct measure on the risk in the treated population is not feasible, spontaneous reporting could offer an approximation of the frequency of the adverse reaction in the treated population, provided that reasonably valid data can be obtained to evaluate the reporting rate in the context of product use. However, the well know biases that affects reporting of suspected adverse reactions may provide misleading results. For instance, the introduction of a risk minimisation measure in response to a safety concern detected in the post-authorisation phase of a medicinal product may raise awareness regarding selected adverse reactions which ultimately may result in an increased reporting rate. In these circumstances an analysis of spontaneous reporting may lead to the erroneous conclusion that the intervention was ineffective. Decreasing reporting rates over time may also lead to the erroneous conclusion that the intervention was effective.

XVI.B.5. Coordination

If several products (herein referred to as “generics”, of the same active substance are available in a market there should be a consistent approach in the use of additional risk minimisation measures coordinated and overseen by the SFDA. When a coordinated action for a class of products is needed a harmonised approach should be agreed if appropriate. Under these circumstances advanced planning should ensure that the effectiveness of risk minimisation measures (see XVI.B.4.) can be considered for each individual product as well as for the products collectively.

XVI.B.6. Quality systems of risk minimisation measures

Although many experts may be involved in developing and implementing risk minimisation measures, the final responsibility for the quality, accuracy and scientific integrity of those measures and the plan describing them lies with the marketing authorisation holder and its QPPV in the KSA

The marketing authorisation holder is responsible for updating the RMP when new information becomes available and should apply the quality principles detailed in Module I. Tracked versions of the RMP should be submitted to facilitate regulatory assessment. These records, the RMP and the associated risk management systems, as well as any documents on risk minimisation measures may be subject to audit or inspection.

The marketing authorisation holder should ensure appropriate version control of the risk minimization tools in order to ensure that all healthcare professionals and patients receive up-to-date risk minimisation tools in a timely manner and that the tools in circulation are consistent with the approved product information. To this purpose the market authorisation holders are encouraged to keep track of the receipt of any risk minimisation tools. These records may be subject to audit and inspection.

The marketing authorisation holder should ensure that mechanisms for reporting the results of studies or analyses for evaluation of the effectiveness of risk minimisation measures are documented. These may be subject to audit or inspection.

XVI.C. Operation within KSA

XVI.C.1. The SFDA

The SFDA should monitor and evaluate the outcome of risk minimisation measures, including additional risk minimisation 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 post-authorisation safety studies which aim to evaluate the effectiveness of risk minimisation measures (see Module VIII).

The SFDA is responsible for the oversight at national level of the implementation of additional risk minimisation measures imposed as a condition of the marketing

authorisation for the safe and effective use of a medicinal product in the KSA. For those risk minimisation measures introduced after the initial marketing authorisation, the SFDA should ensure prompt consideration and agreement of the interventions with the marketing authorisation holder.

The SFDA may facilitate harmonization of the implementation of risk minimisation tools for generic products of the same active substance. When additional risk minimisation measures are considered necessary for generic medicinal product(s) based on safety concerns related to the active substance, the risk minimisation measures applicable to the generic product(s) should be aligned with those for the reference medicinal product. Additional risk minimisation 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.1.2. Marketing authorisation applicant or holder

The applicant or marketing authorisation holder should clearly define the objectives of any proposed additional risk minimisation measure and the indicators to assess their effectiveness. Any additional risk minimisation 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 marketing authorisation holder should provide information regarding the status of implementation of additional risk minimisation measures as agreed with the SFDA and keep them informed of any changes, challenges or issues encountered in the implementation of the additional risk minimisation measures. Any relevant changes to the implementation of the tools should be agreed with the SFDA before implementation.

For generic products the applicant or marketing authorisation holder 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 minimise the burden on the healthcare systems.

For generic products, the effectiveness of risk minimisation measures should be assessed by the marketing authorisation holders in close cooperation with the SFDA. Where formal studies are justified, joint studies for all medicinal products involved are strongly 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 marketing authorisation holder. Recording of specific product details would still be important to enable rapid identification of any new safety hazard with a particular product.

The marketing authorisation holder shall monitor the outcome of risk minimisation measures which are contained in the RMP. General principles for effectiveness evaluation are provided in XVI.B.3..

The applicant or marketing authorisation holder should report the evaluation of the impact of additional risk minimisation activities when updating the RMP (see V.B.11.4.).

The applicant or marketing authorisation holder should report in the Periodic Safety Update Report (PSUR) the results of the assessment of the effectiveness of risk minimisation measures which might have an impact on the safety or risk-benefit assessment (see VII.B.5.16.5. and VII.C.5.5). The applicant or marketing authorisation holder 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.1.3. Healthcare professionals and patients

Healthcare professionals and patients hold no legal obligations with respect to the implementation of the pharmacovigilance legislation. Nonetheless the cooperation of healthcare professionals and patients is paramount to the success of educational programmes and/or controlled access programmes in order to optimise the risk-benefit

balance. It is desirable that they give careful consideration to any additional risk minimisation measure which may be introduced for the safe and effective use of medicines.

XVI.C.2. Impact of risk minimisation measures effectiveness on RMP/PSUR

PSUR and RMP updates should include a summary evaluation of the outcome of specific risk

minimisation measures implemented to mitigate important risks in the KSA. In the RMP, the focus should be on how this informs risk minimisation and/or pharmacovigilance planning. In the PSUR, there should also be evaluation of how the implemented measures impact on the safety profile and/or risk-benefit balance of the product. In general, the focus should be on information which has emerged during the reporting period or since implementation of the most recent risk minimisation measure(s) in the KSA. Where there is parallel submission of a PSUR and a RMP update, the use of a common content Module should be considered (see GVP Modules V and VII).

Results of the assessment(s) of the effectiveness of risk minimisation measures should always be included in the RMP. As part of this critical evaluation, the marketing authorisation holder should make observations on factors contributing to the success or weakness of risk minimisation measures. This critical analysis may include reference to experience outside the KSA, when relevant. The evaluation of the effectiveness of risk minimisation measures should focus on whether these have succeeded in minimising risk. This should be analysed using a combination of process and outcome indicators, as described in XVI.B.3.. It may be appropriate to distinguish between risk minimization measures implemented at the time of initial marketing authorisation and those introduced later in the post-authorisation phase. When presenting the evaluation of the effectiveness of a risk minimisation measure, the following aspects should be considered:

1. The evaluation should provide context by a) briefly describing the implemented risk minimization measure(s), b) defining their objective(s), and c) outlining the selected process and outcome indicators.

2. The evaluation should incorporate relevant analyses of the nature of the adverse reaction(s)

including its severity and preventability. Where appropriate logistical factors which may impact on clinical delivery of the risk minimisation measure should also be included.

3. The evaluation should include an examination of the delivery of the risk minimisation measures in routine clinical practice, including any deviation from the original plan. Such an evaluation may include the results of drug utilisation studies.

4. Outcome indicators (i.e. adverse reaction frequency and/or severity; other safety-related outcomes) should normally be the key endpoint when assessing the attainment of risk minimisation measures objectives.

Proposals for changes to enhance risk management should be presented in the regional appendix of the PSUR (see VII.C.5.). The RMP should be updated to take account of emerging information on the effectiveness of risk minimisation measures.

In general, the frequency of RMP updates should be proportionate to the risks of the product. In general, the focus of RMP updates should be on the risk minimisation measures and in providing updates on the implementation of those measures where applicable. If there is a consequential change to the summary RMP, this should also be highlighted in the cover letter. Changes to the product information should not be proposed via a standalone RMP update but rather a variation application should be submitted. A PSUR can also result directly in an update to product information (if PSURs are being submitted by the marketing authorisation holder for a given generic product).

XVI. Appendix 1. Key elements of survey methodology

Surveys are systematic methods of collecting primary data directly from a sample of participants from a larger population. These are conducted in order to characterise the larger population and may be cross-sectional (one-time only) or longitudinal (repeated over time).

In the context of the evaluation of the effectiveness of risk minimisation measures a survey can be conducted to evaluate understanding, knowledge and behaviour resulting from

educational interventions in a specified target population with respect to the safety and risk management of a medicinal product.

The survey methodology might not be the most appropriate approach for the evaluation of behaviour, since surveys collect and analyse self-reported data from healthcare professionals and patients. Furthermore, participation in a survey in itself may introduce behaviour changes or may not be representative of the target users given that participation is more likely amongst engaged healthcare professionals and/or more motivated or educated individuals.

As a minimum, the following elements should be considered in the design and implementation of a survey in order to minimise potential biases and to optimise the generalisability of the results to the intended population:

1. Sampling procedures and recruitment strategy;
2. Design and administration of the data collection instrument (s);
3. Analytical approaches;
4. Ethics, privacy, and overall feasibility of a study.

XVI.App1.1. Sampling procedures and recruitment strategy

In any survey, the sampling frame and recruitment of participants may be subject to selection bias leading to a study population that is not similar to, or representative of, the intended population in one or more aspects. Furthermore, it should be considered that a bias cannot be eliminated only by increasing the sample frame, sample size and response rate. Bias can be minimised by selecting the optimal sampling frame, taking into account age, sex, geographical distribution and additional characteristics of the study population. Bias can also be minimised by assuring the sample contains appropriate diversity to allow stratification of results by key population characteristics (e.g., by oversampling a small but important subgroup). Key elements to be considered in the sampling frame include age, gender, geographical distribution, and additional characteristics of the study population.

For example, in a physician survey, the strategy for randomly selecting the study sample should consider whether a general random sample would be sufficient or if the sample should be stratified by key characteristics such as specialty, type of practice (e.g., primary

care, specialist ward, academic institution). In a patient survey, income and education, medical condition(s), chronic vs acute use, should be considered. In addition to the overall representativeness of the target population the recruitment strategy of a survey should give careful consideration of the potential recruitment sources. For the recruitment of healthcare professionals, sponsor lists, web panels, professional and learned societies may represent feasible approaches. However, their representativeness for the intended target population of physicians needs to be carefully reviewed for each study. For patient recruitment the relevant clinical setting, existing web-panels, and patient advocacy groups should be considered. A recruitment strategy should be designed while accounting for the 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 influences on the representativeness of the sample.

XVI.App1.2. Design and administration of the data collection instrument(s)

Data collection approaches in a survey may vary from in-person interview, testing, and measurement or collection of biological samples as for routine clinical practice, to telephone interview, web-based or paper-based questionnaires. Audio computer-assisted self-interviewing (A-CASI), interactive voice response systems (IVRS), or mixed mode approaches may also be appropriate. The choice of the most suitable data collection approach will depend on the target population characteristics, the disease and the treatment characteristics and the data to be collected.

Each data collection approach will require the ad hoc design of one or more specific instruments. Nonetheless general design considerations that may apply to all instruments include the following:

- Burden to participant: e.g. length or duration, cognitive burden, sensitivity to participant;
- Clarity and sequence of questions: e.g. use of unambiguous language, minimising assumptions, starting with the most important questions and leaving sensitive questions until later;

- Completeness of responses: e.g. structure questions in order to lead to a single unambiguous answer, allow for choices such as “unknown” or “don’t know”;
- Layout of data collection instrument: e.g. clear flow, technology-assisted guides (avoid patterns, reminders for non-response and visual images);
- Testing and revision of instrument: e.g. formal testing using cognitive pre-testing such as one-to-one interviews, probing questions, interview guide or trained interviewer, and “think aloud” process;
- Incentives to improve response rate: e.g. fed back aggregated data to the survey participants.

XVI.App1.3. Analytical approaches

The key analytical elements of a survey should include:

- Descriptive statistics, such as:
 - The percentage of participants responding correctly to knowledge questions;
 - Stratification by selected variable;
 - Data on no-response or incomplete response;
- Comparison of responders and non-responders characteristics (if data available);
- Comparison of responders and overall target population characteristics.

When survey results are weighted, the following key points should be considered:

- Differences in selection probabilities (e.g. if certain subgroups were over-sampled);
- Differences in response rates;
- Post-stratification weighting to the external population;
- Clustering.

Examples of stratified analyses of physician’s survey include the following:

- Specialty of physician;
- Geographic location;
- Receipt of any educational material;
- Volume of prescribing.

XVI.App1.4. Ethics, privacy and overall study feasibility

Ethical and data privacy requirements are not harmonised across international authority, with notable differences in national (or regional) processes. National (or regional) differences may exist regarding the appropriateness of providing incentives to survey participants. There may also be privacy considerations in allowing contact with physicians based on a prescriber list that is held by a pharmaceutical company.

The overall feasibility assessment of a study is a key step in the successful implementation of a survey. For clinical-based data collection, key elements of such an assessment include:

- Gathering information on site and characteristics of study population (patients or healthcare professionals);
- Estimating reasonable study sample size, the number of sites required to achieve the sample size, and approximate length of the data collection period (e.g. based on estimated patient volume, frequency of patient visits, and expected patient response rate);
- Evaluating site resources and interest in the study.

Key elements of a feasibility assessment may be different for other study designs (e.g. web-based recruitment and data collection) and for physician assessments.

XVI.App.II. Educational materials

XVI. App. II.1. Introduction

Educational programmes are additional risk minimisation 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 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.

This appendix to GVP Module XVI provides guidance for MAH on the submission of draft education materials to the SFDA as well as guidance on the assessment of such materials, in particular as regards the format and content.

XVI. App II.2. Principles for educational materials

The following principles apply to educational materials:

- The need for educational materials will be agreed during a regulatory procedure, at the moment of the initial marketing authorisation or in the post-authorisation phase.
- Any educational material should focus on the risk minimisation objectives.
- It should focus on the specific safety concerns and provide clear statements and concise messages describing actions to be taken in order to prevent and minimise these risks.
- It should not be combined with promotional materials for the marketing of the medicinal product. Educational materials should be drafted in the official language(s) as required by the SFDA.
- When the need for educational material is agreed, the dissemination of the educational material is mandatory. The modalities for dissemination and the target audience are determined by the SFDA.
- The MAH should provide a proposal of the target population of the material.
- The MAH should exercise version control and ensure that it disseminates only the latest agreed version of the educational material.

XVI. App II.3. Submission of educational materials

The draft educational material should be submitted to the SFDA as follows:

- with a submission cover letter including information on: – the contact point of the MAH and, if applicable, another organisation to which it has subcontracted the submission (at least names and e-mail addresses);
 - detailed implementation plan for the educational material:
 - target populations;
 - dissemination method;
 - intended dissemination time;
 - estimated date of launch of the product (in the case of a new marketing authorisation).
- as documents in a common open text-processing electronic format of the proposed materials in language(s) required by the SFDA;
- the intended lay-out and, where applicable, images and graphic presentations of the information (e.g. pictures, charts, diagrams, video).

If the submission concerns an update of educational material previously agreed by the SFDA, the changes to the agreed material should be highlighted.

XVI. App II.4. Format of educational materials

The format of educational material should include the following:

- invented name of the medicinal product followed by the active substance(s) and/or therapeutic class in brackets. However, the invented name should only appear where strictly necessary and the number of times the invented names appears in the educational material should be limited. If there is educational material applicable to several products from different marketing authorisation holders, the educational material should refer to the active substance only and a list of the invented names in the KSA should be annexed;
- if necessary, mention of the different presentations of the product, e.g. the different pharmaceutical forms, the strengths, the routes of administration;
- the title line "Important Risk Minimisation Information for <Healthcare Professionals, Patients>" to clarify the purpose of the educational material;
- an additional title line identifying the type of educational material, e.g. administration guide, checklist for prescribing, alert card, educational leaflet for the patient;

- thereafter 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 and therefore it is advised to be read carefully before prescribing/dispensing/administering the product;
- if the medicinal product is under additional monitoring (see Module X, which will be released), the black symbol should be included next to the medicinal product name or active substance name, along with the explanatory standard statement for additional monitoring;
- bullet points should be used wherever appropriate to present the information clearly;
- materials should be kept as brief as possible, however, if the educational material is long, an introductory text summarising the key messages should be added and an index may be included;
- for version control, the version number and the date of agreement of the material by the SFDA in the format of “<month> <year>” on each sheet of the educational material, unless the type of educational material requires an appropriate exceptions (e.g. a video should have this information appearing at its beginning and end).

If the logo of the MAH appears, the logo should appear only once in each educational material, preferably on the last page. If it however appears on the first page, the logo should not be larger than the document title. No product logos or slogans should be used.

XVI. App II.5. Content of educational materials

The reference documents to be used in the preparation of educational materials are the agreed risk management plan (RMP) (including its annexes), product information (SPC and PIL) and the conditions of the marketing authorization. The educational material should contain the key elements as agreed with the SFDA in an appropriate format and layout. The SPC and/or PIL may be attached to the educational material and disseminated together; or the educational material may contain a reference to the website of the SFDA when SPC and/or PIL are made publicly available on the website. References to other websites for “more information” will usually not be accepted unless it refers to the SPC/PIL.

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 with important data to support the implementation and hence effectiveness of the RMM.

Images and graphic presentations of the information should only be used when text alone is insufficient to adequately convey the key element(s) and should not be promotional.

The scope of the information in the educational material should be limited to the key elements agreed with the SFDA. Additional information such as efficacy data, comparisons of safety with other medicinal products or statements which imply that the medicine is well tolerated or that adverse reactions occur with a low frequency should not be included. Referring to other medicinal products outside the scope of the educational material is not allowed.

A statement encouraging the reporting of any suspected adverse reaction to the SFDA or to the MAH should be included.

XVI. App II.6. 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 SPC, the PIL and the summary of the RMP may be referred to.