Saudi Pharmacovigilance Guideline of Registered Medicines

Version 2.1
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Version 2.1

Drug Sector
Saudi Food & Drug Authority
Kingdom of Saudi Arabia

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Introduction

1. Legal Basis and Framework for Pharmacovigilance:

Pharmacovigilance has been defined by the World Health Organization as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem. The legal framework for pharmacovigilance of pharmaceutical products for human use in the community is given in the law of pharmaceutical products and pharmaceutical institutions number (M/31) dated in 1/6/1425H and the council of ministers decision number 31 dated 24/1/1428H in addition to the Council of Minister Directive number (168) dated 24/6/1423H.

The legislation listed above describes the respective obligations of the MAH (MAH) and of the Saudi Food & Drug Authority (SFDA) to set up a system for pharmacovigilance in order to collect, collate and evaluate information about suspected adverse reactions. All relevant information should be shared between the SFDA and the MAH, in order to allow all parties involved in pharmacovigilance activities to assume their obligations and responsibilities. This requires an intensive exchange of information between the MAH and the SFDA as well as procedures to avoid duplication, maintain confidentiality and ensure the quality of the systems and data.

The requirements explained in these guidelines are based on the International Conference for Harmonization (ICH) and the European Medicine Evaluation Agency (EMEA) guidelines, where these exist, but may be further specified or contain additional requests in line with the legislation of the SFDA. Pharmacovigilance activities come within the scope of the criteria of quality, safety and efficacy, as new information is accumulated on the medicinal product under normal conditions of use in the marketing situation. Pharmacovigilance obligations apply to all authorized medicinal products in Saudi Arabia.

This guidance is required to include technical requirements for the electronic exchange of pharmacovigilance information in accordance with internationally agreed formats.

2. Roles & Responsibilities of Various Parties:

2.1. The SFDA

In accordance with the legislation, SFDA has established a pharmacovigilance system for the collection and evaluation of information relevant to the risk-benefit balance of medicinal products. The SFDA continually monitors the safety profile of the products available in Saudi Arabia and takes appropriate action where necessary and monitors the compliance of MAHs with their obligations with respect to pharmacovigilance. The SFDA should ensure that MAHs implement, when appropriate, Risk Management Plans to effectively monitor and manage risks associated with the safety of their products.
2.2. The Marketing Authorisation Holder (MAH)

The MAH ensure that it has an appropriate system of pharmacovigilance and risk management in place in order to assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken, when necessary.

The roles and responsibilities of the MAH include but not limited to the following:

1. Establish and maintain a system to collect, collate, and evaluate pharmacovigilance data.
2. Meet legal obligations for reporting of suspected adverse reactions.
3. Meet legal obligations regarding the preparation and the submission of periodic Safety Update Reports.
4. Respond fully to requests from SFDA for additional information necessary for the evaluation of the benefits and risks of a medicinal product.
5. Ensure the marketing authorisation is maintained and reflects the latest information.

2.3. 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 (see chapter I.3) leading to recommendations on action at the request of the SFDA for products available in Saudi Arabia. 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 National Pharmacovigilance Center (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.
PART I

Guidelines for Marketing Authorisation Holders
1. General Principles

1.1. Roles and Responsibilities of the MAH and the Qualified Person Responsible for Pharmacovigilance (QPPV)

The MAH should ensure that it has an appropriate system of pharmacovigilance in place in order to assume responsibility and liability for its products on the market and to ensure that appropriate action may be taken when necessary. The MAH should therefore ensure that all information relevant to the risk-benefit balance of a medicinal product is reported to the SFDA fully and promptly in accordance with the legislation.

When submitting an application for a marketing authorisation, the Applicant, in preparation for the role and responsibilities as MAH, should submit a description of the pharmacovigilance system and submit proof that the services of a Qualified Person Responsible for Pharmacovigilance, hereafter referred to as the QPPV, are in place (see chapter I.2).

The MAH should have permanently and continuously at his disposal a QPPV, residing in Saudi Arabia.

Each company (i.e. Applicant/MAH or group of MAHs using a common pharmacovigilance system) should appoint one QPPV responsible for overall pharmacovigilance for all medicinal products for which the company holds authorizations within Saudi Arabia (see chapter I.2).

The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfill the responsibilities and tasks of the post. The name and 24-hour contact details of the QPPV and back-up procedures to ensure business continuity and continued fulfillment of pharmacovigilance obligations should be notified to the SFDA.

1.1.1. The Role and Responsibilities of the Qualified Person Responsible for Pharmacovigilance:

The QPPV is responsible for:

- Establishing and maintaining/managing the MAH’s Pharmacovigilance system.
- Having an overview of the safety profiles and any emerging safety concerns in relation to the medicinal products for which the MAH holds authorisations;
- Acting as a single contact point for the SFDA on a 24-hour basis.

It is recognised that this important role may impose extensive tasks on the QPPV, depending on the size and nature of the pharmacovigilance system and the number and type of medicinal products for which the company holds authorisations. The QPPV may therefore delegate specific tasks, under supervision, to appropriately qualified and trained individuals, e.g. 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.

In case of absence of the QPPV, the MAH should ensure that all responsibilities are undertaken by an adequately qualified person. This person should also reside in Saudi Arabia.
The QPPV should have oversight of the pharmacovigilance system in terms of structure and performance and be in a position to ensure in particular the following system components and processes, either directly or through supervision:

- the establishment and maintenance of a system which ensures that information about all suspected adverse reactions and concerns about product quality which are reported to the personnel of the MAH, and to medical representatives, is collected and collated in order to be Submitted to SFDA in Saudi Arabia;

- the conduct of continuous overall pharmacovigilance evaluation during the post-authorisation period (see chapter I.8);

- the ensuring that any request from the SFDA for the provision of additional information necessary for the evaluation of the benefits and the risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned;

- the provision to the SFDA of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation studies and data from sources described in chapter I.5;

- the coordination of the preparation and submission to SFDA of ADR reports, including reports arising from company-sponsored post-authorisation safety studies, Periodic Safety Update Reports (PSURs) and individual case safety reports (ICSRs).

The oversight referred to above should cover the functioning of the MAH’s pharmacovigilance system in all relevant aspects, including quality control and assurance procedures, standard operating procedures, database operations, contractual arrangements, compliance data (e.g. in relation to the quality, completeness and timeliness for expedited reporting and submission of Periodic Safety Update Reports), audit reports and training of personnel in relation to pharmacovigilance.

The QPPV should also act as the MAH’s contact point for pharmacovigilance inspections or should be made aware by the MAH of any inspection, in order to be available as necessary.
1.1.2. Responsibilities of the MAH in Relation to the QPPV

The MAH should adequately support the QPPV and ensure that there are appropriate processes, resources, communication mechanisms and access to all sources of relevant information in place for the fulfillment of the QPPV’s responsibilities and tasks.

The MAH should ensure that there is full documentation covering all procedures and activities of the QPPV and that mechanisms are in place to ensure that the QPPV may receive or seek all relevant information. The MAH should also implement mechanisms for the QPPV to be kept informed of emerging safety concerns and any other information relating to the evaluation of the risk-benefit balance. This should include information from ongoing or completed clinical trials and other studies the MAH is aware of and which may be relevant to the safety of the medicinal product, as well as information from sources other than the specific MAH, e.g. from those with whom the MAH has contractual arrangements.

The MAH should ensure that the QPPV has sufficient authority

- to implement changes to the MAH’s pharmacovigilance system in order to promote, maintain and improve compliance; and
- to provide input into Risk Management Plans (see Chapter I.3) and into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and, as appropriate, communication to Patients and Healthcare Professionals).

The MAH should assess risks with potential impact on the pharmacovigilance system and plan for business contingency, including back-up procedures (e.g. in case of non-availability of personnel, adverse reaction database failure, failure of other hardware or software with impact on electronic reporting and data analysis).

1.2. Contractual Arrangements

The MAH may transfer any or all of the pharmacovigilance tasks and functions, including the role of the QPPV, to another person(s) or organisation, but the ultimate responsibility for the fulfillment of all pharmacovigilance obligations and the quality and integrity of this always resides with the MAH. In such cases, it is the responsibility of the MAH to ensure that detailed and clear documented contractual arrangements for meeting pharmacovigilance obligations are in place between MAH(s) and persons or organisations involved in the fulfillment of pharmacovigilance obligations and to provide SFDA with information on such arrangements in line with the requirements set out in chapter I.2. The contracted person(s) or organisation should implement quality assurance and quality control and accept to be audited by or on behalf of the MAH.

In cases of contractual arrangements between MAHs in relation to co-marketing of separately authorised medicinal products which are identical in all aspects apart from their invented names, these arrangements should include measures to avoid the duplicate submission of Individual Case Safety Reports (e.g. literature reports) to SaudiVigilance.
2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections

2.1. Introduction

This Chapter sets out the framework for implementation, in the context of the revised pharmaceutical legislation, of the monitoring of compliance with pharmacovigilance obligations and of pharmacovigilance inspections. In the same context it sets out the information to be supplied in the application giving a detailed description of the pharmacovigilance system of the MAH and proof that the MAH has the services of QPPV and the necessary means for the notification of adverse reactions.

2.1.1. Roles of the MAH

The MAH should ensure that they have an appropriate system of pharmacovigilance in place in order to assure responsibility for their products on the market and to ensure that appropriate action can be taken, when necessary. This includes the MAH having at its disposal permanently and continuously an appropriately qualified person responsible for pharmacovigilance residing in Saudi Arabia, and the establishment of a system of pharmacovigilance.

2.1.2. Roles of the SFDA

The roles of the SFDA are described in section 2.3.

2.1.3. Detailed Description of the Pharmacovigilance System to Be Included in the Marketing Authorisation Application

The Applicant for a marketing authorisation is required to provide a detailed description of the system of pharmacovigilance and, where appropriate, of the risk management system which the Applicant will introduce. This Chapter addresses the detailed description of the pharmacovigilance system that should be supplied with the application dossier and supporting documentation that the Applicant should maintain and supply to the SFDA on request. The description of the risk management system, which includes the product-specific pharmacovigilance activity, is addressed in chapter I.3.

2.1.4. Proof of the Services of a QPPV and of the Necessary Means to Notify Adverse Reactions, to be Included in the Marketing Authorisation Application

The Applicant is required to provide proof that they have the services of a QPPV and the necessary means for the notification of any adverse reaction occurring either in Saudi Arabia or abroad.
2.2. Detailed Description of the Pharmacovigilance System

2.2.1. Location in the Marketing Authorisation Application and Update of the Detailed Description

The detailed description of the pharmacovigilance system, including the proof of the availability of the services of the QPPV and the proof that the MAH has the necessary means for the collection and notification of any adverse reaction, should be provided in the application dossier.

The detailed description should comprise an overview of the pharmacovigilance system providing information on the key elements of that system. Where aspects of the system such as the organisational arrangements are particular to the product rather than the main system of the MAH/company (MAH or a group of MAHs sharing the same pharmacovigilance system) this should be indicated in a product-specific addendum.

The detailed description should be supported by documentation maintained by the company.

Updates to the information provided in the detailed description of the pharmacovigilance system should be made as type II variations.

2.2.2. Statement of the MAH and the QPPV Regarding their Availability and the Means for the Notification of Adverse Reactions

The Applicant should provide a signed statement from the MAH and the QPPV to the effect that the Applicant has their services available as QPPV and has the necessary means for the collection and notification of any adverse reaction occurring either in Saudi Arabia or other country. This statement may make reference to the detailed description of the pharmacovigilance system (see Chapter I.2, Section 2.3), indicate what is already in place, and confirm which items will be put in place before the product is registered in Saudi Arabia.

2.2.3. Elements of the Detailed Description of the Pharmacovigilance System

All MAHs are required to have an appropriate system of pharmacovigilance in place. The detailed description of the pharmacovigilance system should include the following elements, as applicable, and be set out in a structured manner consistent with this list. Additional important elements pertinent to a specific situation, should be added:

2.2.3.a. Qualified Person Responsible for Pharmacovigilance (QPPV)

- The name of the QPPV, the business address and contact details should be provided in the Marketing Authorisation Application form. Companies might, for example, use a 24-hour telephone number through which the QPPV or their back-up can be reached, diverting it to the appropriate person according to availability.
- A summary Curriculum Vitae of the QPPV with the key information relevant to their role (main qualifications, training and experience).
- A summary of the job description of the QPPV.
- A description of the back-up procedure to apply in the absence of the QPPV.
2.2.3.b. Organisation

- Identification and location of the company units or other organisations where the principal and global pharmacovigilance activities are undertaken (in particular those sites where the main databases are located, where Individual Case Safety Reports (ICSRs) are collated and reported and where PSURs (Periodic Safety Update Reports) are prepared and processed for reporting to the SFDA).

- High-level organisation chart(s) providing an overview of the global and Saudi Arabia pharmacovigilance units and organisations (identified above) and, illustrating the relationships between them, with affiliate/parent companies and contractors. The chart(s) should show the main reporting relationships with management and clearly show the position of the QPPV within the organisation. Individual names of people should not be included. Licensing partnerships are usually product-specific and should be indicated in a product-specific addendum in the application for that product, unless a partnership is a consistent feature of the company’s organisation across most products.

- A brief summary of the pharmacovigilance activities undertaken by each of the organisations/units identified above.

- Flow diagrams indicating the flow of safety reports of different sources and types. These should indicate how reports/information are processed and reported from the source, to the point of receipt by the SFDA.

2.2.3.c. Documented Procedures

An essential element of any pharmacovigilance system is that there are clear, written procedures in place. The following list indicates topics that should usually be covered by these written procedures. The detailed description should indicate for which of these topics there are written procedures in place, but should not list the procedure titles per se. A procedure may cover one or more of the topics or one topic may have one or more procedures depending on its complexity and the organisation of the company. Care should be taken to ensure that quality control and review are appropriately addressed in the various processes and reflected in the relevant procedures.

- The activities of the QPPV and the back-up procedure to apply in their absence;
- The collection, processing (including data entry and data management), quality control, coding, classification, medical review and reporting of ICSRs:
  - Reports of different types:
    - Organised data collection schemes (solicited), unsolicited, clinical trials, literature
    - The process should ensure that reports from different sources are captured:
      - Saudi Arabia and other countries, healthcare professionals, sales and marketing personnel, other MAH personnel, licensing partners, Competent Authorities, compassionate use, patients, others;
  - The follow-up of reports for missing information and for information on the progress and outcome of the case(s);
  - Detection of duplicate reports;
  - Expedited reporting;
  - Electronic reporting;
- Periodic Safety Update Reports (PSURs):
  - The preparation, processing, quality control, review (including medical review) and reporting;
• Global pharmacovigilance activities applying to all products: Continuous monitoring of
the safety profile of authorised medicinal products (product-specific risk management
systems and pharmacovigilance planning are covered in Chapter I.3.):
  • Signal detection and review;
  • Risk-benefit assessment;
  • Reporting and communication notifying SFDA and healthcare professionals of
    changes to the risk-benefit balance of products, etc;
• Interaction between safety issues and product defects;
• Responses to requests for information from regulatory authorities;
• Handling of urgent safety restrictions and safety variations;
• Meeting commitments to SFDA in relation to a marketing authorisation;
• Global pharmacovigilance activities applying to all products (signal detection, evaluation,
  reporting, communication etc.). (Product-specific risk management systems and
  pharmacovigilance planning are covered in Chapter I.3.);
• Management and use of databases or other recording systems;
• Internal audit of the pharmacovigilance system;
• Training;
• Archiving.

The detailed description of the pharmacovigilance should indicate the processes for which written
procedures are available. A list and copies of the global and Saudi Arabian procedures should be
available within three days on request by the SFDA. Any additional local procedures should be
available to respond to specific requests.

2.2.3.d. Databases

A listing of the main databases used for pharmacovigilance purposes (e.g. compilation of safety
reports, expedited/electronic reporting, signal detection, sharing and accessing global safety
information) and brief functional descriptions of these should be provided including a statement
regarding the validation status of the database systems.

A statement should be included regarding the compliance of the systems with the internationally
agreed standards for electronic submission of adverse reaction reports.

A copy of the registration, of the QPPV, with the Saudi Vigilance system and identification of the
process used for electronic reporting to the SFDA.

There should be an indication of the responsibility for the operation of the databases and their
location (with reference to the locations identified under Chapter I.2, Section 2.3.b above).

2.2.3.e. Contractual Arrangements with Other Persons or Organisations Involved in
the Fulfilment of Pharmacovigilance Obligations

Links with other organisations such as co-marketing agreements and contracting of
Pharmacovigilance activities should be outlined. The company should identify the major
subcontracting arrangements it has for the conduct of its pharmacovigilance activities and the main
organisations to which it has subcontracted these (in particular where the role of the QPPV, the
electronic reporting of ICSRs, the main databases, signal detection, or the compilation of PSURs is
subcontracted).

A brief description of the nature of the agreements the company establishes with co-marketing
partners and contractors for pharmacovigilance activities should be provided. Co-licensing or co-
marketing arrangements should be identified and the distribution of the major responsibilities
between the parties made clear.
Since co-licensing or co-marketing arrangements are mainly product-specific any information on these may be provided in a product-specific addendum, in the applicable Marketing Authorisation Application. Likewise if subcontracting is product-specific this should be indicated in a product specific addendum.

2.2.3.f. Training

Staff should be appropriately trained for performing pharmacovigilance related activities. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel or clinical research staff. Provide a brief description of the training system and indicate where the training records, Curricula Vitae (CVs) and job descriptions are filed.

2.2.3.g. Documentation

Provide a brief description of the locations of the different types of pharmacovigilance source documents, including archiving arrangements. Reference can be made to the organisation charts provided under Chapter I.2, Section 2.3.b above.

2.2.3.h. Quality Management System

Provide a brief description of the quality management system, making cross-reference to the elements provided under the above Sections. Particular emphasis should be placed on organisational roles and responsibilities for the activities and documentation, quality control and review, and for ensuring corrective and preventive action.

A brief description of the responsibilities for quality assurance auditing of the Pharmacovigilance system, including auditing of sub-contractors, should be provided.

2.2.3.i. Supporting Documentation

The MAH should ensure that the pharmacovigilance system is in place and documented.

An essential feature of a pharmacovigilance system is that it is clearly documented to ensure that the system functions properly, that the roles and responsibilities and required tasks are clear to all parties involved and that there is provision for proper control and, when needed, change of the system.

Documentation supporting the pharmacovigilance system (and its detailed description) may be required during the pre-authorisation period, or post-authorisation, for purposes such as assessment or inspection.

2.3. Monitoring of Compliance by the SFDA

SFDA will monitor MAHs for compliance with pharmacovigilance regulatory obligations. Furthermore, SFDA will take appropriate regulatory action in cases of non-compliance as required. Article 37 of the law of pharmaceutical products and pharmaceutical institutions number (M/31) dated 1/6/1425H sets out the roles of the SFDA with respect to the imposition of penalties for infringement of that Regulation or regulations adopted pursuant to it.

Set out below is an outline of how compliance monitoring should be performed. In this context compliance monitoring relates to activities that are separate to inspection activities and are carried out separately to them or as a prelude or follow-up to inspection. Where compliance monitoring
raises concerns these should be highlighted. Deficiencies identified during compliance monitoring may lead to an inspection request.

SFDA will ensure that a system of pharmacovigilance is in place within MAHs through scrutiny of the detailed description of pharmacovigilance, procedures, safety reports and through pharmacovigilance inspections.

2.3.1. QPPV

SFDA will maintain a list of QPPVs for MAHs within Saudi Arabia. This list will include business address and contact details (including out of hours contact).

2.3.2. Availability of Pharmacovigilance Data

SFDA should monitor (e.g. by assessment of the detailed description of the pharmacovigilance system and when inspections are carried out) that pharmacovigilance data are collated and accessible by the MAH in Saudi Arabia.

2.3.3. Change in the Evaluation of the Risk-Benefit Balance of a Product

One of the key responsibilities of MAH is to immediately notify the SFDA of any change in the balance of risks and benefits of their products. Any failure to do so may pose a significant threat to public health. Any evidence of failure to notify such changes will result in consideration of enforcement action by the SFDA.

2.3.4. Expedited Adverse Reaction Reporting

Requirements for expedited reporting of ICSRs are given in Chapter I.4. Non-compliance with expedited reporting may include complete failure to report, delayed reporting (i.e. submission beyond 15 days) and submission of reports of poor quality (particularly where evidence suggests that this results from inadequate company follow-up of individual cases). Failure to comply with electronic reporting requirements will be monitored.

Methods available to SFDA for prospective monitoring of compliance with expedited reporting of adverse reactions could be:

- Monitoring adverse reaction reports received from MAHs against other sources to determine complete failure to report.
- Monitoring the time between receipt by MAH and submission to SFDA to detect late reporting.
- Monitoring the quality of reports. Submission of reports judged to be of poor quality may result in the follow-up procedures of MAH being scrutinised.
- Monitoring that all adverse reactions that are kept in an electronic format are compatible with SFDA’s Pharmacovigilance data base.
- Checking of Periodic Safety Update Reports (PSURs) to detect under-reporting (e.g. of expedited reports).
- Checking interim and final reports of post-authorisation safety studies to ensure that all qualifying serious reports have been submitted within 15 days.
- At inspection there may be a review of a sample of reports on the MAH database to assess the quality of data, determine whether the relevant reports have been expedited and are included on the Saudi Vigilance database, and to confirm that procedures are in place to follow up reports.
2.3.5. Periodic Safety Update Reports (PSURs)

PSURs are important pharmacovigilance documents. They provide an opportunity for MAHs to review the safety profile of their products and ensure that the Summary of Product Characteristics (SPC) and Package Leaflet are up to date. They also provide the SFDA with a valuable source of pharmacovigilance data. For these reasons the SFDA place great importance on compliance with periodic reporting. Non compliance may include:

- Non-submission: Complete non-submission of PSURs, submission outside the correct cycle or outside the correct time frames (without previous submission of a type II variation), non-restart of the cycle of submission when necessary.
- Incorrect format of the document: Report not in accordance with Chapter I.6.
- Omission of information required by Chapter I.6 particularly in the following sections of the report: Update of Regulatory Authority or MAH Actions taken for Safety Reasons, Changes to Reference Safety Information, Patient Exposure and Presentation of Individual Case Histories.
- Poor quality reports: Poor documentation of adverse reactions or insufficient information provided to perform a thorough assessment in the Presentation of Individual Case Histories section, new safety signals not or poorly assessed in the Overall Safety Information section, misuse not highlighted, absence of use of standardised medical terminology (e.g. MedDRA).
- Company core data sheet (CCDS) or SPC: Where changes have been made to the CCDS or SPC since the submission of the last PSUR, the covering letter does not highlight the differences between the CCDS and the SPC.
- Previous requests from SFDA not addressed: Submission of a report where previous requests from SFDA have not been addressed (e.g. close monitoring of specific safety issues).

2.3.6. Information Requested by SFDA

No fixed time frames are laid down in Saudi legislation or guidelines for responding to a request for information from SFDA. This reflects the fact that the appropriate time frame will depend mainly on the urgency of the pharmacovigilance issue and its potential impact on public health. The SFDA will ensure that all requests for information from MAHs have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. SFDA will liaise with MAHs regarding the appropriate deadline, as required. Failure of MAHs to provide the necessary information/data within the deadline may be considered as non-compliance.

2.3.7. Submission of Safety Variations

Saudi legislation and guidelines do not specify deadlines for submission of safety variation applications. As with responding to requests for information from SFDA, deadlines for submission of safety variations will depend on the urgency and potential public health impact of the pharmacovigilance issue. The SFDA will ensure that requests for safety variations have a clearly stipulated deadline and this deadline should be appropriate to the complexity and urgency of the issue. The SFDA will liaise with MAHs regarding the appropriate deadline, as required. Failure of MAHs to submit the variation application within the deadline may be considered as non-compliance.
2.3.8. Submission of follow-up measures

Saudi legislation and guidelines do not specify deadlines for the submission of follow-up measures following the granting of a Marketing Authorisation. The timeframe for submission of follow-up measures should be clearly stated in a letter of undertaking signed by the Applicant.

Compliance with the provisions of these measures will be monitored. These include:

- Conditional marketing authorisations;
- Marketing authorisations under exceptional circumstances;

and the specific obligations or follow-up measures as applicable to these. Normal marketing authorisations may also include follow-up measures.

Non-compliance may include:

- Complete non-submission of data, including non-submission of specific obligations before the annual re-assessment;
- Submission of data after the deadline agreed in the letter of undertaking from the company (without previous agreement from the SFDA);
- Failure to implement a specific obligation;
- Failure to implement a follow-up measure;
- Poor quality of a report requested as a follow-up measure;
- Poor quality of a report requested as a specific obligation;
- Failure to implement an urgent provisional measure.

2.3.9. Post-Authorisation Safety Studies

Because of the objectives of safety studies there is considerable potential for safety signals to arise or changes in the balance of risks and benefits of products to be identified. Therefore, expedited reporting and submission to SFDA of interim and final study reports from such studies has an important role in protecting public health. Where appropriate, SFDA will scrutinize protocols prior to initiation of safety studies. SFDA should check that relevant adverse reaction reports from safety studies are expedited and monitor the submission of interim and final study reports. Guidance on post-authorisation safety studies is available in Chapter I.7.

2.3.10. Provision of Additional Data on Studies

As part of their pharmacovigilance system, companies are required to have processes in place to screen all studies for information on safety or lack of efficacy and to report on this when required (see also Chapters I.1 and I.8). The SFDA will monitor this by comparison of information received from different sources and in the course of inspections.

2.4. Pharmacovigilance Inspections

To ensure that MAHs comply with pharmacovigilance regulatory obligations and to facilitate compliance, SFDA will conduct Pharmacovigilance inspections. Inspections will be routine as well as targeted to MAHs suspected of being non-compliant. The results of an inspection will be routinely provided to the inspected MAH who will be given the opportunity to comment on the findings. The results will be used to help MAHs improve compliance and may also be used as a basis for enforcement action. The scheduling and conduct of these inspections will be driven by routine programs and by risk analysis criteria.
2.4.1. Conduct of Inspections

The SFDA will conduct inspection of the MAH’s Pharmacovigilance system in the place where the MAH’s Pharmacovigilance activities is located. Where an additional facility (e.g. a database) in another country requires inspection, the inspection will also be carried out by the SFDA.

2.4.2. Routine Inspections

Routine inspections are carried out by the SFDA. The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet their regulatory obligations for authorised products. These inspections may be requested with one or more specific products selected as examples for which specific information can be traced and verified through the various processes, in order to provide practical evidence of the functioning of the pharmacovigilance system of the MAH and their compliance with their regulatory obligations.

In cases where the SFDA has carried out, or intends, within the required timeframe, to carry out, an inspection covering the scope of that requested, this inspection will suffice and its results will be made available to the Advisory and/or Registration Committee.

Where the pharmacovigilance system of a MAH has not been inspected previously, the SFDA will carry out and report on an inspection of the system within 4 years of the placing on the market of the first authorized product by that MAH. Where the system has previously been inspected, re-inspection will take place at intervals. The timing of the first inspection and any further inspection will be determined on the basis of risk analysis criteria.

The SFDA will determine a program for inspection in relation to authorised products. These inspections will be prioritised based on the potential risk to public health, the nature of the products, extent of use, number of products that the MAH has on the Saudi market, etc and risk factors such as those identified under Chapter I.2, Section 4.3. This programme will be separate from any targeted inspection, but if a targeted inspection takes place it may replace the need for one under this programme dependent on its scope.

2.4.3. Targeted Inspections

Targeted inspections may be conducted as and when the trigger is recognised and the SFDA determines that inspection is the appropriate course of action.

Targeted inspections may arise when one or more of the following arise:

- Triggers for the inspection are identified which do not relate to specific concerns about a product’s safety or actual non-compliance, e.g.:
  - The MAH has not previously been inspected;
  - The MAH has placed their first product on the Saudi market;
  - The MAH has recently been or is involved in a merger or takeover process;
  - The MAH has changed their system significantly (e.g. new database system, contracting out of reporting activities).

- Triggers for the inspection are identified which relate to specific concerns about a product’s safety or actual non-compliance, e.g. significant issues relating to:
  - Delays in carrying out or failure to carry out specific obligations or follow-up measures relating to the monitoring of product safety, identified at the time of the marketing authorisation;
• Delays in expedited or periodic reporting;
• Incomplete reporting;
• Submission of poor quality or incomplete PSURs;
• Inconsistencies between reports and other information sources;
• Change in risk-benefit balance;
• Failure to communicate change in risk-benefit balance;
• Previous inspection experience;
• Information received from other authorities;
• Poor follow-up to requests for information from the SFDA;
• Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to the SFDA;
• Product withdrawal with little or no advance notice to the SFDA.

The above are examples and other issues may trigger a targeted pharmacovigilance inspection. The presence of a trigger will not always lead to the conduct of an inspection.

2.4.4. Pharmacovigilance System Inspections

These inspections are designed to review the systems, personnel, facilities in place and their compliance with pharmacovigilance obligations. They may use products as examples to test the system. They may be routine or targeted.

2.4.5. Product-Specific Inspections

These inspections focus specifically on a given product and are usually targeted as a result of triggers that have been identified (see Chapter I.2, Section 4.3).

2.4.6. Requesting and Reporting of Inspections

Inspection requests are prepared by the SFDA. These requests are presented to the advisory Committee for adoption and once adopted are carried out by the SFDA.

2.4.7. Inspections of Contractors and Licensing Partners

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

2.4.8. Inspections outside Saudi Arabia

These may be routine or targeted. They will be included in routine inspections when considered appropriate, particularly where the main pharmacovigilance centre and databases etc. are located outside Saudi Arabia for the MAH product(s) in question. They will be included in targeted inspections whenever this is considered appropriate by SFDA.

2.4.9. Fees for Inspections Requested by the SFDA

An inspection fee(s) and inspectors’ expenses, where applicable, will be charged in accordance with the SFDA Fees system.
2.4.10. Procedures for Pharmacovigilance Inspections

Procedures for pharmacovigilance inspection will be prepared by the Pharmacovigilance department, the Good Clinical Practice (GCP) Inspection Team in association with pharmacovigilance inspectors and will be updated as needed.

These procedures will be adopted and published in line with the policies and procedures of the SFDA on such documents.

2.4.11. Unannounced Inspections

It is anticipated that the majority of inspections will be announced. However, on occasions, it may be appropriate to conduct unannounced inspections or to announce an inspection at short notice.

2.4.12. Inspection Reports

Each inspection will result in an inspection report, prepared in accordance with an agreed format. The inspection report will be made available to the pharmacovigilance department. A copy of the report will be made available to the licensing and compliance & enforcement departments if there is a violation. The inspection report will be made available to the MAH.

2.4.13. Follow-up of Inspection Findings

Where an inspection reveals non-compliances the MAH will be required to prepare a remedial action plan to correct the non-compliances and avoid their recurrence. The MAH may be required to provide reports and where necessary evidence of the progress and completion of the action plan. There may be re-inspection at an appropriate time to verify the progress and success of these remedial actions.

2.5. Regulatory Action

Under Saudi legislation, to protect public health, SFDA are obliged to implement pharmaceutical legislation and to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance regulatory 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 non-compliance but any instance of non-compliance may be referred for enforcement action.

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

- **Education and Facilitation**
  MAHs may be informed of non-compliance and advised on how this can be remedied.

- **Inspection**
  Non-compliant MAHs may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved.

- **Warning**
  SFDA may issue a formal warning reminding MAHs of their pharmacovigilance regulatory obligations.

- **Naming non-compliant MAHs**
  SFDA will consider a policy of making public a list of MAHs found to be seriously or persistently non-compliant.
• Urgent Safety Restriction
• Variation of the Marketing Authorisation
• Suspension of the Marketing Authorisation
• Revocation of the Marketing Authorisation
3. Requirements for Risk Management Systems

3.1. 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 small numbers of subjects in clinical trials, 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 risk-benefit is judged positive for the target population. However, not all actual or potential risks will have been identified when an initial authorisation is sought. In addition, there may be subsets of patients for whom the risk is greater than that for the target population as a whole.

Planning of pharmacovigilance activities will be improved if it were more closely based on product specific issues identified from pre- or post-authorisation data and from pharmacological principles. Such planning will also guide the use of electronic data, which are routinely collected within health services to provide rapid investigation of predicted or emerging safety concerns.

The management of a single risk can be considered as having four steps, risk detection, risk assessment, risk minimisation and risk communication. However, a typical individual medicinal product will have multiple risks attached to it and individual risks will vary in terms of severity, and individual patient and public health impact. Therefore, the concept of risk management should also consider the combination of information on multiple risks with the aim of ensuring that the benefits exceed the risks by the greatest possible margin both for the individual patient and at the population level.

This Chapter aims to provide guidance on how MAHs and Applicants should meet the requirements for a description of a risk management system that they will introduce for an individual medicinal product, or a series of medicinal products. This guidance also describes how such a risk management system can be presented to SFDA in the form of a Risk Management Plan.

SFDA legislation requires Applicants/MAHs to provide a description of pharmacovigilance and risk management systems.

The present Guideline provides guidance to Applicants and MAHs in Saudi Arabia on how to meet the requirements for a ‘detailed description of the risk management system’ (see Chapter I.3, Section 2) and the circumstances when it is appropriate (see Chapter I.3, Sections 4 and 14) to provide it. The risks addressed in this guidance are those related to non-clinical and clinical safety. Where the disposal of the product might pose a particular risk because of remaining active substance (e.g. patches) this should also be addressed. The Guideline is applicable to products in both the pre-authorisation and post-authorisation phase.

For the purpose of this guidance, SFDA requires from the applicants/ MAHs to include the following particulars and documents in the application for the authorization of medicinal product for human use:

“a) detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce.”
“b) details of any conditions or restrictions which should be imposed on the supply or use of the medicinal product concerned, including conditions under which the medicinal product may be made available to the patients.”

“c) details of any recommended conditions or restrictions with regard to the safe and effective use of the medicinal product”.

“d) for a period of five years following the initial placing on the market in Saudi Arabia, the SFDA may request that the MAH arrange for specific Pharmacovigilance data to be collected from targeted groups of patients”.

SFDA requires from MAH that a qualified person should be available to answer any inquiry on their Pharmacovigilance program. This qualified person shall be responsible for the following:

“1) ensuring that any request from SFDA for the provision of additional information necessary for the evaluation of the benefits and risks afforded by a medicinal product is answered fully and promptly, including the provision of information about the volume of sales or prescriptions of the medicinal product concerned”;

“2) the provision to the SFDA, of any other information relevant to the evaluation of the benefits and risks afforded by a medicinal product, including appropriate information on postauthorization safety studies”.

The detailed description of a risk management system should be provided in the form of an SFDA Risk Management Plan (SFDA-RMP) in the situations described in Chapter I.3, Section 4. It is strongly recommended that discussions with the SFDA on the need for, and content of, an SFDA-RMP should take place in advance of submission.

3.2. Description of the Risk Management System

A risk management system is 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 interventions. The legislation requires that a description of the risk management system should be submitted when appropriate. This requirement can be met by the submission of an SFDA-RMP in the circumstances detailed in Chapter I.3, Sections 4 and 14.

The aim of a risk management system is to ensure that the benefits of a particular medicine (or a series of medicines) 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 but, by its definition, risk management focuses upon the risk reduction approach. Nevertheless, whenever possible, increases in benefits should also be considered and the characteristics of patients most likely to benefit from treatment should be better defined.

3.3. SFDA Risk Management Plan (SFDA-RMP)

The description of a risk management system should be submitted in the form of an SFDA-RMP. The SFDA-RMP contains two parts:

Part I:
- A Safety Specification,
- A Pharmacovigilance Plan; and

Part II:
- An evaluation of the need for risk minimization activities;
and if there is a need for additional (i.e. non-routine) risk minimization activities

- A risk minimization plan.

Part I of the SFDA-RMP incorporates the Safety Specification, which summarizes the safety profile of the medicinal product at the particular point in time of its life-cycle, and the Pharmacovigilance Plan which is based on the Safety Specification. Chapter I.3, section 6.2.g details the particular SFDA requirements for the safety specification.

In Part II of the SFDA-RMP, on the basis of the Safety Specification, the Applicant/MAH should consider carefully the need for risk minimization activities to be introduced. Risk minimisation activities may be “routine” or “additional” (see Chapter I.3, Section 8). Within the “evaluation of the need for risk minimisation activities”, the Applicant/MAH should discuss fully the use of routine risk minimisation activities and whether there is a need for additional risk minimisation activities. If only routine risk minimisation activities are required there is no need to submit a risk minimisation plan. If additional risk minimization activities are thought necessary, the Applicant/MAH should provide a risk minimisation plan within Part II of the SFDA-RMP. This risk minimisation plan should contain both the routine and additional activities for each safety concern. Every time the SFDA-RMP is updated (see Chapter I.3, Section 14) the Applicant/MAH should reconsider its position vis-à-vis the need for risk minimisation activities and Part II should be updated accordingly.

### 3.4. Situations Requiring an SFDA-RMP

An SFDA-RMP may need to be submitted at any time of a product’s life-cycle – i.e. during both the pre-authorisation and post-authorisation phases. In particular an SFDA-RMP should be submitted:

- with the application for a new marketing authorisation for:
  - any product containing a new active substance;
  - a similar biological medicinal product;
  - a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product.

- with an application involving a significant change in a marketing authorisation (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically - derived product, significant change in indication) unless it has been agreed with the SFDA that submission is not required;
- on request from SFDA (both pre-and post-authorisation);
- on the initiative of an Applicant/MAH when they identify a safety concern with a medicinal product at any stage of its life cycle.

In some circumstances, products which are not in the above categories which are seeking a new authorisation may require an SFDA-RMP:

- Known active substances
- Hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks
- Bibliographical applications
- Fixed combination applications.

For situations where the submission of an SFDA-RMP is not mandatory, the need for it should be discussed with the SFDA well in advance of the submission.
3.5. Location in the Application

An SFDA-RMP submitted at the time of an application for a Marketing Authorisation should be provided in the Marketing Authorisation Application in a separate document allowing circulation to, and evaluation by Pharmacovigilance and risk management experts. It should be accompanied by other relevant documents such as study protocols, where applicable.

Updates to the SFDA-RMP (see Chapter I.3, Section 14) should be presented preferably in a tab-separated dossier and in accordance with the appropriate headings and numberings of the SFDA-CTD format. This should be accompanied by a cover letter, detailing which sections of the SFDA-RMP have been changed, and study reports (if appropriate).

3.6. Safety Specification

The Safety Specification should be a summary of the important identified risks of a medicinal product, important potential risks, and important missing information. It should also address the populations potentially at risk (where the product is likely to be used), and outstanding safety questions which warrant further investigation to refine understanding of the risk-benefit profile during the post-authorisation period. The Safety Specification is intended to help industry and regulators identify any need for specific data collection and also to facilitate the construction of the Pharmacovigilance Plan.

In the SFDA-RMP the Safety Specification will also form the basis of the evaluation of the need for risk minimisation activities and, where appropriate, the risk minimisation plan.

It is recommended that Applicants/MAHs 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. Conversely, for products already on the market with emerging new safety concerns, only a subset of the elements might be relevant.

3.6.1. Non-clinical Part of the Safety Specification

Within the Safety Specification, this section should present non-clinical safety findings that have not been adequately addressed by clinical data, for example:

- Toxicity (including repeat-dose toxicity, reproductive/developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity);
- General pharmacology (cardiovascular, including QT interval prolongation, nervous system);
- Drug interactions;
- Other toxicity-related information or data.

The relevance of the findings to the use in humans should be discussed. If the product is intended for use in special populations, consideration should be given to whether specific non-clinical data needs exist.
3.6.2. Clinical Part of the Safety Specification

3.6.2.a. Limitations of the Human Safety Database

Limitations of the safety database (e.g. related to the size of the study population, study inclusion/exclusion criteria) should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed. Particular reference should be made to populations likely to be exposed during the intended or expected use of the product in medical practice.

In order to assess the limitation of the human safety database, the size of the study population should be detailed using both numbers of patients and patient time (patient-years, patient-months) exposed to the drug. This should be stratified, for relevant population categories such as age and gender, type of study (e.g. randomised controlled trial, open clinical trial, observational study) and any other relevant variable, such as dose, indication and duration of treatment. Limitations of the database should also be presented in terms of the frequencies of adverse drug reactions detectable given the size of the database. The limitations of the database should also be discussed with regard to suspected long-term adverse reactions (e.g. malignancies) when it is unlikely that exposure data is of sufficient duration and latency.

Post-marketing (non-study) exposure:

Where marketing of the medicine has occurred, the applicant / MAH should provide data on patients exposed post-marketing. 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 taken 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.

A more accurate breakdown of drug exposure based on market research should be provided where possible. When deciding which measure to use for exposure data, it is important to consider the way a medicine is used. For example, for medicines 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. The information should be stratified by relevant variables such as age, indication, dose and duration of treatment.

3.6.2.b. Populations Not Studied in the Pre-Authorisation Phase

The Safety Specification should discuss which populations have not been studied or have only been studied to a limited degree in the pre-authorisation phase. The implications of this with respect to predicting the safety of the product in the marketplace should be explicitly discussed.

Limitations of the database should also be presented in terms of the relevance of inclusion and exclusion criteria in relation to the target population, in particular when exclusion criteria are not proposed as contraindications for the drug. 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.

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

- Children;
- The elderly;
- Pregnant or lactating women;
- Patients with relevant co-morbidity such as hepatic or renal disorders;
• Patients with disease severity different from that studied in clinical trials;
• Sub-populations carrying known and relevant genetic polymorphism;
• Patients of different racial and/or ethnic origins.

Post Marketing Experience:

For updates to the Safety Specification, specific reference should be made to how the realised pattern of exposure (including off-label use) has differed from that predicted and from the indication(s) and contraindications in the Summary of Product Characteristics.

Newly identified safety concerns should be mentioned, in particular any issue found in relation to a population not studied in the pre-approval phase should be discussed along with the implications for the Summary of Product Characteristics.

If regulatory action has been taken in relation to a safety concern, this should be mentioned.

3.6.2.c. Adverse Events/Adverse Reactions

This section should list the important identified and potential risks that require further characterization or evaluation.

Identified risks that require further evaluation

More detailed information should be included on the most important identified adverse events/adverse reactions, which would include those that are serious or frequent and that also might have an impact on the balance of benefits and risks of the medicinal product. This information should include evidence bearing on a causal relationship, severity, seriousness, frequency, reversibility and at-risk groups, if available. Risk factors and potential mechanisms should be discussed. These adverse events/adverse reactions should usually call for further evaluation as part of the Pharmacovigilance Plan (e.g. frequency in normal conditions of use, severity, outcome, at-risk groups).

Potential risks that require further evaluation

Important potential risks should be described in this section. The evidence that led to the conclusion that there was a potential risk should be presented. It is anticipated that for any important potential risk, there should be further evaluation to characterise the association.

Presentation of risk data

When the information is available, detailed risk data should be presented according to the following format.

The frequency of important adverse reactions 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. When an accurate frequency is needed for an important adverse reaction, 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 adverse event/adverse reaction 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. Where appropriate, the period of major risk should be identified. Adverse event/adverse reaction incidence rates should be presented for the whole population and for relevant population categories.

For important identified risks, the excess and relative incidence should be given. Excess incidence (in comparison to placebo and active comparator; if available) should be calculated based on the best available evidence (e.g. meta-analytic techniques) for each population (total controlled, total controlled plus open label extension, total study). Time to event data should be summarised using survival techniques which take appropriate account of informative censoring. Cumulative hazard functions may provide a simple visual comparison of the competing risks of different adverse reactions. These data can be stratified by substance (to investigate the difference in the adverse event profile between active and placebo), or by risk factors such as dose, gender or age.

The potential impact of the most important identified and important potential risks should be addressed using for example: strength of evidence, supporting plausibility, nature of evidence and potential public health burden, morbidity and case fatality. Recording this in a structured form will facilitate assessment of the potential significance of a safety concern. Classification of the safety concern by dose, time and risk factors is encouraged. The identification of susceptible patients should receive specific attention, possibly from analysis of cases. It is likely that the adverse reactions will require further evaluation as part of the Pharmacovigilance Plan.

3.6.2.d. Identified and Potential Interactions including Food-Drug and Drug-Drug Interactions

Identified and potential pharmacokinetic and pharmacodynamic interactions should be discussed. 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.

It should be stated which interactions require further investigation.

3.6.2.e. Epidemiology

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

In addition, for important adverse events that may require further investigation, it is useful to review the incidence rate of these events among patients in whom the medicinal product is indicated (i.e. the background incidence rates). Information on risk factors for an adverse event would also be useful to include, if available. 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. This population is also at increased risk of myocardial infarction. If it is suspected that the medicinal product might also cause myocardial infarction, it would be useful to know how many cases would be expected amongst prostate cancer patients (ideally) or men in the same age group, not on the medicinal product.
3.6.2.f. Pharmacological Class Effects

The Safety Specification should identify risks believed to be common to the pharmacological class.

If a risk which is common to the pharmacological class is not thought to be a safety concern with the medicinal product, this should be justified.

3.6.2.g. Additional SFDA Requirements

The Applicant/MAH is requested to discuss the topics below. If the potential is thought to be significant, the topic should be identified as an important potential risk and means for reducing or minimising it discussed in the “evaluation of the need for risk minimization activities”. In this context, “significant” means that there is a reasonable likelihood that it will occur. Where a particular topic is not relevant to the individual medicinal product, this should be stated along with the reason.

Potential for overdose

Special attention should be given in particular cases, e.g. where there is a narrow therapeutic margin, a medicinal product with significant toxicity and/or there is an increased risk of overdose in the target population.

Potential for transmission of infectious agents

The Applicant/MAH should discuss the potential for the transmission of an infectious agent in line with Chapter I.5.

Potential for misuse for illegal purposes

The potential for misuse for illegal purposes should be considered. 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 RMP section “Evaluation of the Need for Risk Minimisation Activities”.

Potential for off-label use

The potential for off-label use should be discussed. 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.

Potential for off-label paediatric use

If the disease or disorder which is being treated or prevented is found in the paediatric population, the potential for off-label paediatric use should be discussed.

3.6.3. Summary

At the end of the Safety Specification a summary should be provided of the:

- Important identified risks;
- Important potential risks; and
- Important missing information.
Based on this summary the Applicant/MAH should provide a Pharmacovigilance Plan and an evaluation of the need for risk minimisation activities (see Template in Annex 5.1.1).

3.7. **Pharmacovigilance Plan**

The Pharmacovigilance Plan should be based on the Safety Specification and propose actions to address the safety concerns identified. Early discussions between SFDA and the Applicant or MAH 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 the Pharmacovigilance Plan will not replace but rather complement the procedures currently used to detect safety signals.

3.7.1. **Routine Pharmacovigilance**

For medicinal products where no special concerns have arisen, routine pharmacovigilance should be sufficient for post-authorisation safety monitoring, without the need for additional actions (e.g. safety studies).

A description of routine Pharmacovigilance activities is covered elsewhere in Part I, which should be consulted in developing the Pharmacovigilance Plan.

3.7.2. **Additional Pharmacovigilance Activities and Action Plans**

For medicinal products with important identified risks, important potential risks, or important missing information, additional activities designed to address these safety concerns should be considered.

Applicants/MAHs should also consider the situations when routine Pharmacovigilance is likely to be inadequate. An example of this might be 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 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 important 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 medicine used in the palliative treatment of metastatic cancer.

The Table I.7.A lists some of the epidemiological activities which might be considered for inclusion in a Pharmacovigilance Plan. Additional Pharmacovigilance activities included in the Pharmacovigilance Plan should be designed and conducted according to the recommendations in the Guidelines for Good Pharmacoepidemiology Practices (GPP)(1). For studies involving children, the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population (see Annex 3.1.3) should be consulted. The responsibility for the scientific value of
study protocols remains with Applicants or MAHs, even if they have been previously discussed with SFDA.

3.7.3. Action Plan for Safety Concerns

Within the Pharmacovigilance Plan the action plan for each safety concern should be presented and justified according to the following structure (see also Annex 5.1.1):

- Safety concern
- Objective of proposed action(s)
- Action(s) proposed
- Rationale for proposed action(s)
- Monitoring by the Applicant/MAH for safety concern and proposed action(s)
- Milestones for evaluation and reporting.

Protocols (draft or otherwise) for any formal studies should be provided. Details of the monitoring for the safety concern in a clinical trial could include: stopping rules, information on the drug safety monitoring board and when interim analyses will be carried out.

Although not explicitly included in this structure, it is also necessary in the SFDA-RMP to explain the decision making processes which will depend on the outcomes of the proposed actions. The possible consequences of the study outcomes should be discussed.

3.8. Evaluation of the Need for Risk Minimisation Activities

On the basis of the Safety Specification, the Applicant/MAH should provide an evaluation of the need for risk minimisation activities.

For each safety concern, the Applicant/MAH should assess whether any risk minimisation activities are needed. Some safety concerns may be adequately addressed by the proposed actions in the Pharmacovigilance Plan, but for others the risk may be of a particular nature and seriousness that risk minimisation activities are needed. It is possible that the risk minimization activities may be limited to ensuring that suitable warnings are included in the product information or by the careful use of labelling and packaging, i.e. routine risk minimisation activities. If an Applicant/MAH is of the opinion that no additional risk minimization activities beyond these are warranted, this should be discussed and, where appropriate, supporting evidence provided.

However, for some risks, routine risk minimisation activities will not be sufficient and additional risk minimisation activities will be necessary. If these are required, they should be described in the risk minimisation plan (see Chapter I.3, Section 9) which should be included in Part II of the SFDA-RMP.

Within the evaluation of the need for risk minimisation activities, the Applicant/MAH should also address the potential for medication errors (see Chapter I.3, Section 8.1) and state how this has been reduced in the final design of the pharmaceutical form, product information and packaging.

As a rule, Applicants/MAHs should always consider the need for risk minimisation activities whenever the Safety Specification is updated in the light of new safety information on the medicinal product. In some circumstances, it may be appropriate to suggest that an additional risk minimisation activity be stopped because experience with the medicinal product suggests that it is no longer necessary for the safe and effective use.
3.8.1. Potential for Medication Errors

Applicants/MAHs are encouraged routinely to consider 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 the medicinal product for marketing, the Applicant needs to take into account potential reasons for medication error. The naming, 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.

If a product has life-threatening potential 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.

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. 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.

Consideration should be given to the prevention of accidental ingestion or other unintended use by children.

Medication errors identified during product development 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 SFDA-RMP and ways of limiting the errors proposed.

3.9. The Risk Minimisation Plan

The risk minimisation plan details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern. When a risk minimisation plan is provided within an SFDA-RMP, the risk minimisation plan should include both routine and additional risk minimization activities. A safety concern may have more than one risk minimisation activity attached to an objective. For example, a possible plan for a known teratogen could have the objective of avoiding any patient taking the drug becoming pregnant. A routine risk minimisation activity might be to emphasise the need for effective contraception in the Summary of Product Characteristics and a recommendation that patients should have a negative pregnancy test before each prescription. One additional risk minimisation activity might be to develop an educational pack to provide information to the patients on the risks of the medicine and the need for contraception. It might also be an activity to limit the pack sizes to one month’s supply of the medicine.

The risk minimisation plan should list the safety concerns for which risk minimisation activities are proposed. The risk minimisation activities, i.e. both routine and additional, related to that safety concern should be discussed. For each safety concern the following headings in the plan will mirror those for safety concerns listed in Chapter I.3, Section 7.3. In addition, for each proposed additional risk minimisation activity, a section should be included detailing how the effectiveness of it as a measure to reduce risk will be assessed (see Annex 5.1.1).
3.10. Risk Minimisation Activities

It is difficult 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. Some of the risk minimisation activities are described in the Table I.3.A at the end of this Chapter, but it is essential that appropriate specialised experts are consulted at all stages and Marketing Authorisation Applicants and Holders are also encouraged to discuss risk minimisation plans with the SFDA early on.

3.10.1. Risk Communication

Accurate and timely communication of emerging data on risk is an essential part of Pharmacovigilance. Risk communication is an important step in risk management as well as a risk minimisation activity. Patients and healthcare professionals need accurate and well communicated information about the risks associated with both the medicinal product, and the condition for which it is being used, so that an informed choice can be made about the most appropriate treatment. The product information in the form of the Summary of Product Characteristics and Patient Information Leaflets is an important means of informing prescribers and patients about the risks associated with a particular medicine but additional materials may be needed. A short list of established media for such communication is given in the Table I.3.A (under Additional Educational Material), but the target audience, levels of detail required to achieve effective results and the most appropriate forms of words will all vary with circumstances. Whereas MAHs may produce educational material to inform and educate Healthcare Professionals and Patients, the requirement to do this will only be included as a condition of the marketing authorisation when it is deemed necessary for the safe and effective use of the medicinal product.

Because of the importance of risk communication it is recommended that appropriate experts are consulted.

3.11. The Marketing Authorisation

Restrictions and conditions within the marketing authorisation may be used as a risk minimisation activity (Table I.3.A). When a marketing authorisation is granted, it will include details of any conditions or restrictions imposed on the supply or the use of the medicinal product, including the conditions under which the medicinal product may be made available to patients. These conditions may also be modified when the marketing authorisation is amended in the post-authorisation phase. This is commonly referred to as the “legal status” of a medicinal product. It may also restrict where the medicine can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist). For medicines only available upon prescription, additional conditions may be imposed by classifying medicines into those available only upon either a restricted medical prescription or a special medical prescription.

SFDA may also make recommendations on conditions or restrictions with regard to the safe and effective use of the medicinal product.

3.12. Ensuring the Effectiveness of Risk Minimisation Activities

The definition of risk management requires assessment of the effectiveness of the interventions forming part of the process. It is clearly desirable that activities which may involve substantial investment of effort and resources should be shown to achieve the desired effects. In addition, as a public health measure it is imperative that alternative methods be adopted should a particular risk minimisation strategy prove ineffective. Assessment of effectiveness will also increase understanding of which activities are most appropriate in addressing specific types of safety concerns.
3.12.1. Assessment of Risk Minimisation

Direct measurement of risk minimisation should be employed whenever feasible. Surrogate measures should be considered when this is not feasible or to provide interim assessments whilst awaiting direct risk minimisation measurements. For example, for measures based on the provision of information to professionals, descriptive studies or surveys which assess whether the information is being effectively communicated might be appropriate. The use of medical databases might also allow direct measures of how uniformly such advice was being adhered to by reviewing, for example, concomitant medication or the results of laboratory tests. Since such studies are likely to be required with increasing frequency, the availability of such databases will be an ever more important factor in risk management. If the prescribing databases are further linked to patient clinical outcome, a study of the adequacy of the prescribing process could be designed to evolve over time into a full risk reduction study.

It is clear that, even when risks are of a type which can be directly measured, ethical and practical considerations may prevent prospective comparison. It may be scientifically difficult to make direct comparison between a situation with and without the intervention to be assessed and may not be achievable in timescales which allow the lessons learned to be used to improve risk management. In particular this will occur when risks associated with long-term exposure or very rare events are to be reduced. For products where a risk minimisation plan has been introduced after some time on the market a comparison with historical data can be made. Notwithstanding the above, Applicants/MAHs should investigate new methodologies for monitoring and assessment.

3.13. Summary of Activities in the SFDA-RMP

The SFDA-RMP should contain an overall summary of the activities detailed for the medicinal product. This should be in two parts:

- Summary of activities for each important safety concern;
- Summary of all activities and their milestones.

The relationship between activities and safety concerns may be clarified by a cross-tabulation of the two categories showing which safety concerns are addressed by each activity (see Annex 5.1.1).

Summary of activities for each safety concern:

This should be a simple table, listing each safety concern and summarising the activities (both Pharmacovigilance and, where appropriate, risk minimisation) which will be taken. Where appropriate, it should provide a cross-reference to the actions in the Pharmacovigilance Plan and the risk minimisation activities for the individual safety concern.

Summary of all activities and their milestones:

This section of the SFDA-RMP for the product should be organised in terms of the actions or activities to be undertaken and their milestones. 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. Timelines and milestones should be included in the summary with a timetable for the submission of findings. In developing these milestones one should consider:

- when it will be possible to detect an adverse reaction with a pre-defined frequency at a predefined confidence level. This frequency should be chosen such as to reflect an acceptable level of risk for patients and public health; or
- when it will be possible to assess with sufficient precision the effect of risk factors associated with the occurrence of an adverse reaction;
• when the results of ongoing or proposed safety studies are expected to be available;
• the seriousness and magnitude of the risk for which risk minimisation activities are being proposed. Evaluation of the effectiveness of the activities will need to be carried out earlier and more frequently if the risk is very serious.

3.14. Submission of Updated SFDA-RMP Documents

As additional information on the safety of a medicinal product becomes available, the Safety Specification and other sections of the SFDA-RMP should be updated accordingly. For example, spontaneous reports, clinical trials and pharmacoepidemiological studies may all give rise to safety signals which need to be investigated or the results from a study could provide new information to update the Safety Specification. It may be that, based on the new information, it can be concluded that the safety concern has been resolved and that no further actions are needed beyond routine pharmacovigilance. In other cases, additional activities may be proposed and new milestones should be developed.

The update should include assessment of the effectiveness of the risk minimisation activities within the RMP.

At each update, consideration should be given as to whether new risk minimisation activities are needed. This may be because of a new safety concern or with an existing safety concern because the data suggests that the current strategy is not effective.

Updated SFDA-RMPs are only required for medicinal products where an SFDA-RMP (or similar document) has already been submitted under the conditions in Chapter I.3, Section 4 or required under the terms of the marketing authorisation.

The updated SFDA-RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR) unless other requirements have been laid down as a condition of the marketing authorisation.

In addition, an updated SFDA-RMP should be submitted:

• when new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities;
• within 60 days of an important (Pharmacovigilance or risk minimisation) milestone being reached or the results of a study becoming available;
• at the request of the SFDA.

A cover letter should be submitted with the updated SFDA-RMP briefly summarising the changes from the previous SFDA-RMP.

Where no changes to any part of the SFDA-RMP have occurred since the last submission, a letter stating this, and the date of the last SFDA-RMP submission should be sent. In this circumstance it is not necessary to re-submit the SFDA-RMP with the letter.

Periodic Safety Update Reports

A summary of any amendments made to the SFDA-RMP, prior to the data lock point of the Periodic Safety Update Report (PSUR), should be included in the PSUR (see Addendum to ICH E2C Clinical Safety Data Management. Periodic Safety Update Reports for Marketed Drugs, Section 2.8.3 (see Annex 4).
TABLE I.3.A: METHODS FOR RISK MINIMISATION

Risk minimisation activities can be divided into those where a reduction in risk is achieved primarily through the provision of information and education and those which seek to control the use of the medicine. When it is obvious that a risk minimisation activity will be needed post-authorisation, consideration should be given to piloting the activity during the development phase to see the effectiveness and suitability. When this is done, the outcome should be provided in the risk minimisation plan under the appropriate action.

1. Provision of Information

Provision of information to Healthcare Professionals and/or Patients on the specific risks of a product and the measures on how to reduce them is an essential activity of risk management. This provision of information may be confined to information contained within the Summary of Product Characteristics (SPC) and Package Leaflet (routine risk management) or may be through the use of additional educational material (additional risk management). The need for additional material beyond the Summary of Product Characteristics and Package Leaflet will depend upon the risk and should be considered on a case-by-case basis. Experts in risk communication should be consulted as appropriate.

1.1 Additional Educational Material

The need for additional educational material and the form in which it should be provided will depend upon the specific safety concern. The aim of a specialised educational program for healthcare professionals and/or patients is to:

- Enhance understanding of the specific risk(s);
- Enhance understanding of measures to reduce either the frequency or severity of adverse reactions;
- Enhance early detection and treatment (if applicable) of an adverse reaction;
- Enhance patient information, awareness and provide information on the need and use of additional precautions.

The educational program may include but is not limited to the following materials:

- Direct Healthcare Professional Communications;
- Physician’s Guide to Prescribing;
- Pharmacist’s Guide to Dispensing;
- Checklists for assessing comprehension, knowledge, attitudes, and/or desired safety behaviours about the risk(s). These should be tailored to the target audience (e.g. physicians, pharmacists or patients);
- Checklists for actions before prescribing or dispensing;
- Patient Information Brochures;
- Specific training programmes.

The choice of media may also need to be considered (written, audio or video) as well as the use of drawing/symbols to improve understanding. For medicines where the target population may include a larger proportion of visually impaired patients, the use of Braille or audio media should be given special consideration. Pre-testing materials in the target audience(s) is highly desirable to help ensure good comprehension and acceptance of the communication method and contents. A variety of testing methods such as readability testing, focus groups or surveys could be used.

Specific training programmes may be considered in certain circumstances. However, it is unlikely that prescription/dispensing of the medicine can be limited to people who have undertaken such a programme.

The above educational materials should be in strict compliance with the contents of the SPC and the Package Leaflet and must be agreed with the SFDA.
2. Legal Status of a Medicine

It is possible that controlling the conditions under which a medicine may be made available could reduce the risks associated with its use or misuse. This might be achieved by control of either who may be permitted to prescribe or dispense a medicine or by controlling who, or the conditions under which a patient, may receive a medicine.

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 the medicinal product may be made available to Patients. This is commonly referred to as the “legal status” of a medicinal product. Typically it includes information on whether or not the medicinal product is subject to medical prescription. It may also restrict where the medicine can be administered (e.g. to a hospital) or by whom it can be prescribed (e.g. specialist).

Although the use of legal status is not an activity that can be used directly by an Applicant for the purposes of risk reduction, the Applicant could request the SFDA to consider a particular legal status.

For medicines only available upon prescription, additional conditions may be imposed by classifying medicines into those available only upon either a restricted medical prescription or a special medical prescription. When considering classification 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 restriction to use in a hospital environment may in practice ensure that the medicine 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 medicine can be safely administered. For example the term “clinic” has different connotations depending upon the country. For this reason, the type of equipment needed may be specified rather than a location, e.g. “use in a setting where resuscitation equipment is available.”

For classification as subject to special medical prescription the following factors should 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.
3. Control at Pharmacy Level

The control of dispensing is another potential activity for risk management. Pharmacists who are well informed about the risks of a medicine can help educate the Patient and provide an additional level of protection.

4. Control of Prescription Size or Validity

Limiting the validity of a prescription is another activity for risk management in the situation where decision to prescribe depends upon the result of a test which is only valid for a specific time.

Limiting the number of units prescribed is another risk minimisation activity. This can be useful if regular testing or review is needed. By limiting the number of units, the patient 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. If this strategy is adopted, it is a pre-requisite that the appropriate pack size is available and that supply issues are addressed. 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.

5. Informed Consent and other Patient Aspects

In a clinical trial, patients are given information about the possible benefits and risks of the trial medication and any procedures associated with the trial. The Patient signs a form to say that they have been given the information, they understand it and agree to take part in the trial. This is known as informed consent. It has potential as a risk management activity to ensure that patients have been provided with appropriate information regarding the risks of the medicine and appropriate measures to reduce the risks.

6. Restricted Access Programs

In high-risk situations, it may be necessary to restrict access to a medicinal product to those patients who agree to take part in a specific surveillance program.

7. Patient Registries

Patient registries are often suggested as a means of risk management. They have been used (sometimes very successfully) in individual countries to record the results of tests, to ensure that the recommended conditions of use are being adhered to, and control access to a medicine. However, there are possible issues about who controls the registry and the confidentiality of medical data.

Patient registries could be a very useful activity for Pharmacovigilance studies to characterise risks. It is strongly suggested that if a MAH is contemplating the use of a patient registry, this should be discussed with SFDA at a very early stage.
4. Requirements for Expedited Reporting of Individual Case Safety Reports

4.1. Introduction

The obligations of the MAH for recording and reporting suspected adverse reactions associated with a medicinal product for which marketing authorisations are held are given in the law of pharmaceutical products and pharmaceutical institutions number (M/31) dated 1/6/1425H. For suspected adverse reactions requiring expedited reporting, further explanation is provided in this Chapter. Reporting requirements in special situations, including obligations of the Applicant during the period between submission of the Marketing Authorisation application and granting of the Marketing Authorisation, are described in Chapter I.5.

For authorised medicinal products, independent of the authorisation procedure, adverse reactions received from Healthcare Professionals, either spontaneously or through post-authorisation studies, should be reported, regardless of whether or not the medicinal product was used in accordance with the authorised Summary of Product Characteristics (SPC) and/or any other conditions laid down for marketing of the product in accordance with applicable legal requirements. Adverse reactions identified from the worldwide-published scientific literature should also be reported. Electronic reporting of adverse reactions is mandatory, save in exceptional circumstances (see Chapter II.9).

The definitions of ‘suspected adverse reaction’, ‘serious adverse reaction’ and ‘expected/unexpected adverse reaction’ are provided in the Glossary (see Annex 1). In the context of pharmacovigilance, the term adverse reaction is considered as synonymous with suspected adverse reaction and adverse drug reaction.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction and therefore should be reported in expedited manner (see Chapter I.5, Section 9). In addition, such cases should be considered for reporting as product defects if appropriate.

When a MAH receives an Individual Case Safety Report (ICSR) where the invented name of the medicinal product is not specified but the active substance is included in any of the medicinal products for which a marketing authorisation is held, the MAH should assume that the report may relate to their product.

Spontaneous reports of adverse reactions received from Healthcare Professionals should be reported by the MAH if:

- the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; or if
- the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown; or if
- the MAH considers that a causal relationship is at least a reasonable possibility.

If the Healthcare Professional has made an explicit statement that a causal relationship between the medicinal product and reaction has been excluded and the MAH agrees with this, the event should not be reported.

When the MAH is aware that a Healthcare Professional may have reported a reaction to one of their products directly to the SFDA, the MAH should still report the reaction, informing SFDA that the report may be a duplicate of a previous report. In this situation, it is essential for the MAH to provide all the available details including all case identification numbers allocated to the case, in order to aid identification of the duplicate case. For further guidance on reporting of potential
The MAH is expected to validate all adverse reactions reported by Healthcare Professionals to ensure, prior to reporting to the SFDA, that the minimum information required is included in the report:

- An identifiable Healthcare Professional reporter (see Section A.2 “Primary source(s) of information” of ICH E2B(M) (see Annex 4);
  - The reporter may be identified by name or initials, address or qualification (e.g. physician, dentist, pharmacist, nurse), (see Chapter II.4, Section 4). Contact details for a Healthcare Professional should be available for the reporter to be considered as identifiable.
- An identifiable Patient (see Section B.1 “Patient characteristics” of ICH E2B(M) (see Annex 4);
  - The Patient may be identified by initials, patient number, date of birth, age, age group or sex. The information should be as complete as possible (see Chapter II.4, Section 4).
- At least one suspected active substance/medicinal product (see Section B.4 "Drug(s) information" of ICH E2B(M) (see Annex 4);
- At least one suspected adverse reaction (see Section B.2 "Reactions(s)/event(s)” of ICH E2B (M) (see Annex 4).

Reports should be followed-up to obtain additional information relevant to the case as necessary, and relevant follow-up information should be reported to the SFDA (see Chapter II.4, Section 3). All available clinical information relevant to the evaluation of the adverse reaction should be provided (see Chapter II.4, Section 1)

For reports on adverse reactions from Patients/Consumers, see Chapter I.4, Section 3.5.

If ICSRs, which do not qualify for expedited reporting as outlined in this Chapter, provide information that may lead to a change in the known risk-benefit balance for the product, this possible change should be notified to the SFDA without delay.

### 4.2. Reporting Time Frames

The MAH should transmit all ICSRs requiring expedited reporting promptly and no later than 15 calendar days from receipt. This applies to initial and follow-up information.

The date the MAH becomes aware of a case which fulfils the minimum information (see Chapter I.4, Section 1) should be considered day 0. The same applies if new information on the case is received by the MAH, i.e. the reporting time clock begins again for the submission of the follow-up report from the day the MAH receives relevant follow-up information (see also Chapter II.4, Section 3).

The clock for expedited reporting starts (day 0) as soon as the minimum information (see Chapter I.4, Section 1), has been brought to the attention of any personnel of the MAH or an organisation having a contractual arrangement with the MAH, including medical representatives.

For individual cases described in the worldwide scientific literature, the clock starts (day 0) with awareness of a publication containing the minimum information (see Chapter I.4, Section 1) by any personnel of the MAH or an organisation having a contractual arrangement with the MAH, including medical representatives. For further guidance see Chapter II.6.
Contractual arrangements may be made with a person or organisation to perform literature searches and/or report relevant individual cases to SFDA. If another person or organisation is performing these tasks, explicit procedures and detailed agreements should exist between the MAH and this person or organisation to ensure that the MAH is promptly made aware of any individual cases described in the worldwide scientific literature to ensure that the MAH can comply with their reporting obligations.

In general, where the MAH has set up contractual arrangements with a person or organisation for e.g. the marketing of, or research on a medicinal product authorised to this MAH, the clock starts as soon as any personnel of the MAH or the other person/organisation receives the minimum information that constitutes a reportable case. Explicit procedures and detailed agreements should exist between the MAH and the person/organisation to ensure that the MAH can comply with his reporting obligations (see Chapter I.1).

4.3. Requirements by Reporting Source

4.3.1. Spontaneous Reports from Healthcare Professionals

a) Individual Case Safety Reports on adverse reactions occurring within Saudi Arabia

For all medicinal products, the MAH should report, on an expedited basis, all serious adverse reactions occurring within Saudi Arabia, and brought to their attention by a Healthcare Professional, to the SFDA.

For reporting purposes, any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction and therefore should be reported in expedited manner (see Chapter I.5).

Non-serious adverse reactions occurring within Saudi Arabia should only be reported in an expedited manner on request and otherwise in accordance with Chapter I.6 on Periodic Safety Update Reports.

b) Individual Case Safety Reports on adverse reactions occurring outside Saudi Arabia

For all medicinal products, the MAH should report on an expedited basis, all unexpected serious adverse reactions and any suspected transmission via a medicinal product of an infectious agent occurring outside Saudi Arabia.

Serious unexpected adverse reactions and any suspected transmission via a medicinal product of an infectious agent initially reported by a Healthcare Professional and subsequently transmitted by a regulatory authority outside Saudi Arabia to the MAH are also subject to expedited reporting to SFDA by the MAH.

Although not a legal requirement, MAHs are encouraged to also report all expected serious adverse reactions occurring outside Saudi Arabia on an expedited basis to SFDA, provided that reporting takes place electronically in accordance with ICH E2B(M) (see Chapter II.10).

Non-serious adverse reactions occurring outside Saudi Arabia should only be reported in expedited manner on request and otherwise in accordance with Chapter I.6 on Periodic Safety Update Reports.
4.3.2. Reports Published in the Worldwide Literature

Individual case reports from the worldwide literature in accordance with the provisions of Chapter I.4, Section 1 are considered to be reports of which the MAH can reasonably be expected to be aware and have knowledge of.

The MAH is therefore expected to maintain awareness of possible publications by accessing a widely used systematic literature review and reference database (e.g. Medline, Excerpta Medica or Embase) no less frequently than once a week. In addition, company offices are required to be aware of publications in Saudi local journals and bring them to the attention of the QPPV as appropriate.

Cases of adverse reactions from the scientific and medical literature, including relevant published abstracts from meetings and draft manuscripts, should be reviewed to identify individual cases which might qualify for expedited reporting.

As required by legislation, the MAH should report within 15 days published serious adverse reactions associated with the use of the active substance(s) of their medicinal products, as relevant to the categories identified in Chapter I.4, Section 3.1. The procedure for handling of adverse reaction reports published in the worldwide literature is described in Chapter II.6.

If the medicinal product source and/or the invented name is not specified and ownership of the product cannot be excluded on the basis of the active substance(s), formulation or route of administration, the MAH should assume that it is one of their products the publication refers to, although the report should indicate that the specific product source and/or the invented name was not identified.

If multiple medicinal products are mentioned in the publication, a report should be submitted only by the MAH(s) of the product(s) which is (are) identified by the publication’s author(s) as having at least a possible causal associated with the reaction.

4.3.3. Information on Adverse Reactions from the Internet

The MAH should regularly screen websites under their management or responsibility, for potential reports on adverse reactions. The MAH is not expected to screen external websites for information on adverse reactions. However, if a MAH becomes aware of an adverse reaction on any other website the MAH should review the case and determine whether it should be reported in expedited manner in accordance with Chapter I.4, Sections 3.1 and 3.5.

The MAH should consider utilising their websites to facilitate adverse reaction collection, e.g. by providing adverse reaction forms for reporting or by providing appropriate contact details for direct communication. In relation to such reported adverse reactions, identifiability of the reporter and Patient refers to the existence of actual people (see Chapter I.4, Section 3.1).

4.3.4. Reports from Organised Data Collection Systems

Reporting requirements for cases derived from organised data collection systems (which include clinical trials, post-authorisation studies, registries, post-authorisation named-patient use programmes, other patient support and disease management programmes, surveys of Patients or Healthcare Providers, and information gathering on efficacy or patient compliance) differ depending on whether they are derived from interventional or non-interventional studies.
a) Interventional Studies

Adverse reactions arising from interventional studies on medicinal products for Human Use should be reported. The investigator shall report all serious events immediately to the sponsor except for those that the protocol or investigator’s brochure identifies as not requiring immediate reporting. Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluation shall be reported to the sponsor according to the reporting requirements within the time periods specified in the protocol. The investigator shall supply the sponsor and the Ethics Committee with any additional requested information, notably for reported deaths of a subject.

The sponsor shall keep detailed records of all adverse events and he shall submit these records on request to the SFDA. The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to SFDA and Ethics Committee, and in any case no later than seven days after his knowledge of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days. The sponsor shall ensure that all relevant information about suspected serious unexpected adverse reactions shall be reported to the SFDA and the Ethics Committees as soon as possible but within a maximum of fifteen days of his first knowledge. The sponsor shall provide SFDA and the Ethics Committees every year with a listing of all suspected serious adverse reactions which have occurred over this period.

For reporting of adverse reactions in the Periodic Safety Update Reports (PSURs), see Chapter I.6.

b) Non-interventional Studies

Serious adverse reactions arising from non-interventional studies should be reported on an expedited basis according to the same criteria and timelines as adverse reactions reported spontaneously by Healthcare Professionals (see Chapter I.4, Section 1); this includes any suspected transmission via a medicinal product of an infectious agent. All adverse reactions, i.e. also non-serious ones, should be included in the final study report. For reporting of adverse reactions in the Periodic Safety Update Reports (PSURs), see Chapter I.6. For further information on post-authorisation safety studies see Chapter I.7.

4.3.5. Reports from Patients and Other Consumers

When information is received directly from a Patient/Consumer suggesting that an adverse reaction may have occurred, the MAH should attempt to obtain the Patient's consent to contact the Healthcare Professional involved for further information. When such a report has been confirmed by the Healthcare Professional, it should be documented as a spontaneous report from a Healthcare Professional and reported according to Chapter I.4, Sections 1 and 3.1. When a Consumer submits medical documentation that supports the occurrence of the adverse reaction, this should be considered sufficient to report the individual case if it provides the minimum information (see Chapter I.4, Section 1).

For requirements to reflect Consumer reports in Periodic Safety Update Reports see Chapter I.6, Section 3.7. For requirements in relation to reporting of outcomes of use of medicinal products during pregnancy, originating from Consumers, see Chapter I.5, Section 4.

Medically unconfirmed adverse reactions should not be reported to the SFDA on expedited basis.

4.3.6. Reports from Other Non-Medical Sources

If a MAH becomes aware of a case report from non-medical sources other than those mentioned in Chapter I.4, Section 3.5, e.g. the lay press or other media, every attempt should be made to obtain the minimum information that constitutes an individual case (see Chapter I.4, Section 1) and to follow-up the case as for reports from a Patient/Consumer (see Chapter I.4, Section 3.5).
4.4. Data Elements for the Report

The principles in the ICH-E2D Guideline and ICH E2B(M) Guideline (see Annex 4) should be followed. Detailed aspects related to the preparation of ICSRs and the applicable data elements are defined in Part II.

For the minimum information constituting a case and for the standards relating to the electronic transmission of an ICSR, see Chapter I.4, Section 1 and Chapter II.2.

It is essential for the MAH to provide as many data elements as possible for cases of adverse reactions to facilitate assessment (see Chapter II.4, Sections 1 and 2). The MAH is expected to follow-up all reports of serious adverse reactions to their medicinal product(s) to obtain comprehensive information where available. Additional information not available at the time of the initial report should be provided in the form of follow-up reports (see Chapter I.4, Section 1 and Chapter II.4, Section 3).

The suspect, interacting and/or concomitant active substance(s)/invented name of the suspect product(s) should be reported in accordance with ICH-E2B(M) (see Annex 4) and as outlined in Chapter II.4, Section 1. The MAH should report ICSRs to the SFDA in English language.

The MAH may comment on the causal relationship between the suspect product(s) and the reaction(s) reported and should provide the criteria on which he has made the assessment in field B.4.k.18 “Relatedness of drug to reaction(s)/event(s)” of ICH E2B(M).

In situations where ICSRs impact on the known risk-benefit balance of a medicinal product, the MAH should indicate in a separate letter to the SFDA what action is proposed in relation to the marketing authorisation, the Summary of Product Characteristics and Patient Information Leaflet. This should in addition be recorded in field B.5.4 “Sender’s comments” of ICH-E2B(M).

4.5. Method of Reporting

Electronic reporting of adverse reactions is mandatory, save in exceptional circumstances. The requirements for electronic transmission of ICSRs to be followed are explained in accordance with Part II.
5. Requirements for Reporting in Special Situations

5.1. Introduction

Adverse reactions should be reported according to the requirements outlined in Chapter I.4, regardless of whether or not the medicinal product was used in accordance with the authorised Summary of Product Characteristics (SPC) and/or any other conditions laid down for the marketing of the product.

In addition to routine expedited and periodic reporting requirements as laid out in Chapters I.4 and I.6, the MAH should be aware of the following additional reporting requirements relating to worldwide experience with the medicinal product:

- Reporting in the period between the submission of the marketing authorisation application and the granting of the marketing authorisation;
- Reporting following suspension or withdrawal of the marketing authorisation for safety of commercial reasons;
- Reporting of outcomes of use of a medicinal product during pregnancy;
- Reporting of adverse reactions during breastfeeding;
- Reporting of data on use of medicinal products in children;
- Reporting from compassionate/named-patient use;
- Reporting of lack of efficacy;
- Reporting of suspected transmission of infectious agents;
- Reporting in relation to overdose, abuse and misuse;
- Reporting of medication errors;
- Reporting in the event of a public health emergency.

5.2. Reporting in the Period between the Submission of the Marketing Authorisation Application and the Granting of the Marketing Authorisation

In the period between submission of the marketing authorisation application and the authorisation, information that could impact on the risk-benefit balance may become available to the Applicant. It is the responsibility of the Applicant to ensure that this information is immediately submitted to the SFDA.

5.3. Reporting Following Suspension or Withdrawal of the Marketing Authorisation for Safety or Commercial Reasons

Reporting requirements remain following suspension of the marketing authorisation of a medicinal product (see Chapters I.4 and I.6). Where a marketing authorisation is withdrawn or revoked, the former MAH is encouraged to continue to report in line with Chapter I.4 to e.g. facilitate review of delayed onset adverse reactions and retrospectively notified cases. It may be appropriate to continue submission of PSURs after withdrawal or revocation of the marketing authorisation. An agreement should be made on a case-by-case basis with the SFDA.
5.4. Reporting of Outcomes of Use of a Medicinal Product During Pregnancy

The MAH should follow-up all reports from Healthcare Professionals relating to pregnancies where the foetus may have been exposed to one of his medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure). Where reports originate from Consumers, reasonable attempts should be made to follow-up via the Patient’s Healthcare Professional. When a Consumer submits medical documentation that supports the occurrence of a suspected adverse reaction, this should be considered sufficient to report the case if it provides the minimum information (see Chapter I.4, Section 1).

When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering the possibility of foetal exposure (i.e. medicinal products taken before conception need to be considered) (see Annex 3.1.2).

Individual cases with an abnormal outcome in association with a medicinal product should be reported on an expedited basis, following the reporting requirements outlined in Chapter I.4 and in accordance with the Guideline on Exposure to medicinal products During Pregnancy: Need for Post-Authorisation Data (see Annex 3.1.2) and the ICH E2B(M) Guidelines (see Annex 4).

This refers especially to:

- Reports of congenital anomalies in the foetus/child;
- Reports of foetal death and spontaneous abortion; and
- Reports of adverse reactions in the neonate that are classified as serious.

Other cases, i.e. reports of termination of pregnancy without information on congenital malformation and reports of pregnancy exposure without outcome data, should not normally be reported on an expedited basis.

In certain circumstances, the MAH may be requested to treat any reports of pregnancy exposure as cases requiring expedited reporting, e.g. pregnancy exposure to products contraindicated in pregnancy because of a high teratogenic potential.

Information on exposure to medicinal products during pregnancy should include dates of exposure and, as far as possible, details of the period of gestation at the time of exposure, specified by the method of assessment and expressed as weeks and/or days. This information is necessary to establish a possible causal relationship between the adverse event(s) reported and exposure to the product.

It is also important to collect information on pregnancies, which have a normal outcome. Not infrequently, pregnant women or Healthcare Professionals will contact either the MAH or SFDA requesting information on the teratogenic potential of a medicinal product and/or experience of use during pregnancy (see Annex 3.1.2).

Expeditied reports together with other reports on outcome of exposure during pregnancy should also be included in the Periodic Safety Update Report (PSUR) (see Chapter I.6) together with aggregated data on the overall exposure and details of normal/abnormal outcomes. Reports from prospective registries should also be included and evaluated in the PSUR.

If, at any time, the MAH identifies, or becomes aware of, a signal of a possible teratogenic effect (e.g. through a cluster of similar abnormal outcomes) SFDA should be informed on an expedited basis. This also applies to possible signals arising from Consumer reports for which medical confirmation has not (yet) been obtained.
5.5. Reporting of Adverse Reactions during Breastfeeding

Adverse reactions suspected in infants following exposure to a medicinal product from breastfeeding, should be reported in accordance with Chapter I.4.

5.6. Reporting of Data on Use of Medicinal Products in Children

Collection and evaluation of data on exposure of children to medicinal products and associated risks is an important task and specific guidance is therefore included in the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population (see Annex 3.1.3). Exposure of children should also be considered and addressed in the Risk Management Plan (see Chapter I.3).

5.7. Reporting from Compassionate/Named-Patient Use

Compassionate or named-patient use of a medicine should be strictly controlled by the company responsible for providing the medicine and should ideally be the subject of a protocol.

Such a protocol should ensure that the Patient is registered and adequately informed about the nature of the medicine and that both the prescriber and the Patient are provided with the available information on the properties of the medicine with the aim of maximising the likelihood of safe use. The protocol should encourage the prescriber to report any adverse reactions to the company, and to the SFDA, where required.

Companies should continuously monitor the risk-benefit balance of medicines used on compassionate or named-patient basis (subject to protocol or not) and follow the requirements for reporting to SFDA. As a minimum, the requirements laid down in Chapter I.4, Section 1 apply.

For inclusion of experience from compassionate or named-patient use in Periodic Safety Update Reports, see Chapter I.6.

5.8. Reporting of Lack of Efficacy

Reports of lack of efficacy should not normally be reported on expedited basis, but should be discussed in the relevant Periodic Safety Update Report (see Chapter I.6). However, in certain circumstances reports of lack of efficacy should be treated as expedited cases for reporting purposes. Medicinal products used for the treatment of life-threatening diseases, vaccines and contraceptives are examples of classes of medicinal products where lack of efficacy should be considered as cases requiring expedited reporting. Judgement should be used in reporting, considering if other cases qualify for reporting. For example, antibiotics used in life-threatening situations where the medicinal product was not in fact appropriate for the infective agent should not be reported. However, a lifethreatening infection where the lack of efficacy seems to be due to the development of a newly resistant strain of a bacterium previously regarded as susceptible should be reported on an expedited basis.

5.9. Reporting of Suspected Transmission of Infectious Agents

For the purposes of reporting, any suspected transmission of an infectious agent via a medicinal product is also considered a serious adverse reaction and all such cases should be reported in expedited manner in accordance with the criteria outlined in Chapter I.4, whether they occur within or outside Saudi Arabia.
For cases occurring outside Saudi Arabia, the legislation includes this reporting requirement specifically to ensure that such cases are appropriately reported and to avoid failure to report due to interpretation of such cases as expected (e.g. given the manufacturing process). For cases occurring within Saudi Arabia, the legal requirement to report any such transmission in expedited manner is addressed by the reporting requirements for all (i.e. expected and unexpected) serious adverse reactions as Chapter I.4.

For electronic reporting, such cases should be classified as serious in field A.1.5.1, and field A.1.5.2. “Seriousness criteria” should be set to “Other medically important condition (see ICH-E2B(M) in Annex 4).

The requirement to apply MedDRA coding (see Annex 4) is also relevant to the reporting of cases of suspected transmission of an infectious agent.

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 symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. As in the case of suspected adverse reactions and adverse reactions, the terms suspected transmission and transmission are considered synonymous. 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.

Signals arising from case reports on suspected transmission of an infectious agent should be investigated as for other adverse reactions.

Suspected or confirmed quality defect of medicinal products should be reported to the SFDA. Any contamination of a medicinal product should be considered serious and is likely to be classified as a Class 1 or Class 2 Product Defect (see Annex 6).

The potential for transmission of an infectious agent via a medicinal product should also be addressed in the Risk Management Plan (see Chapter I.3).

Any serious adverse events related to the use of medicinal products derived from human blood or human plasma should be reported to SFDA.

medicinal products should also comply with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Products (2).

5.10. Reporting in Relation to Overdose, Abuse and Misuse

The MAH should collect any available information on overdose, abuse and misuse related to his products. Reports of overdose, abuse and misuse should be routinely followed up to ensure that information is as complete as possible with regard to early symptoms, treatment and outcome. The MAH should report cases of overdose, abuse and misuse that lead to serious adverse reactions on an expedited basis in accordance with the requirements in Chapter I.4. This includes cases of intended suicide. The MAH should continuously monitor and evaluate the potential impact of overdose, abuse and misuse on the overall risk-benefit balance of the medicinal product. The potential for overdose, abuse and misuse and the associated risks should also be addressed in the Periodic Safety Update Reports (see Chapter I.6) and the Risk Management Plan (see Chapter I.3).
5.11. Reporting of Medication Errors

The MAH should report cases of medication errors that are associated with serious adverse reactions on an expedited basis in accordance with the requirements in Chapter I.4. Cumulative information on medication errors, resulting in adverse reaction or not, should be discussed in the section of the Periodic Safety Update Report on the overall safety evaluation (see Chapter I.6). The potential for medication errors and their prevention should be addressed in the Risk Management Plan (see Chapter I.3).

Medication errors due to confusion of invented names in relation to authorised products should be reported to SFDA.


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 appropriately notified.
6. Requirements for Periodic Safety Update Reports

6.1. Introduction

A Periodic Safety Update Report (PSUR) is intended to provide an update of the worldwide safety experience of a medicinal product to Competent Authorities at defined time points post-authorisation. At these times, MAHs are expected to provide succinct summary information together with a critical evaluation of the risk-benefit balance of the product in the light of new or changing information. This evaluation should ascertain whether further investigations need to be carried out and whether changes should be made to the marketing authorisation and product information.

This Chapter is consistent with ICH-E2C and the Addendum to ICH-E2C (now ICH-E2C (R), see Annex 4).

Once a medicinal product is authorised in Saudi Arabia, even if it is not marketed, the Marketing Authorisation Holder is required to submit PSURs at 6-monthly intervals. When launch dates are planned, this information should be reflected in the upcoming PSUR.

Once marketed, 6-monthly PSUR submissions should be continued following initial placing on the market in Saudi Arabia and until two full years of marketing experience in Saudi Arabia has been gained. Then, PSURs should be submitted once a year for the following two years and thereafter at 3-yearly intervals.

PSURs should also be submitted upon request of an SFDA at any time after granting of the marketing authorisation.

Moreover, review of the periodicity is also part of the Risk Management Plan and its assessment (see Chapter I.3).

There may be situations where exceptionally the submission of 6-monthly and subsequent yearly PSURs may be re-started, or where other amendments of the periodicity are required. This is further explained in Chapter I.6, Section 2.4.c.

If the MAH considers, on the basis of the data included in the PSUR, that amendment of the Summary of Product Characteristics (SPC) is necessary, a variation application should be submitted with the PSUR, or where this is not possible, a timetable for submission should be proposed at the time of PSUR submission.

6.2. General Principles

6.2.1. General Scope of Information

The main focus of the PSUR should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR. For this purpose, analysis of adverse reaction reports, an overview of cumulative data, safety data from studies and other relevant safety information, as well as follow-up of any Risk Management Plan (see Chapter I.3) should be adequately addressed in the PSUR. Reports of lack of efficacy (see Chapter I.5, Section 8), specifically for medicinal products used in the treatment of life-threatening conditions and for certain other medicinal products, e.g. contraceptives and vaccines, may represent a significant hazard and in that sense may give rise to a safety concern. These types of cases should be discussed within the PSUR (see Chapter I.6, Section 3.9.a). Moreover, data from pregnancy experience and outcome should also be discussed.
An increase in the frequency of Individual Case Safety Reports (ICSRs) for known adverse reactions is considered as relevant new information. Although increased reporting should be discussed in the PSUR, it is not possible to provide specific guidance as to what constitutes increased reporting or what method should be used for quantifying this. The MAH should provide details of the methods that have been used. Judgement should be used in such situations to determine whether the data reflect a meaningful change in occurrence of adverse reactions or in the safety profile and whether an explanation can be proposed for such a change (e.g. population exposed, duration of exposure).

6.2.2. One Periodic Safety Update Report for Products Containing an Active Substance Authorised to One MAH

It is recommended that information on all indications, dosage forms, routes of administration and regimens for a given active substance for medicinal products authorised to one Marketing Authorisation Holder should be included in a single PSUR, with a single data lock point common for all aspects of product use to facilitate a consistent, broad-based examination of the safety information for the active substance(s) in a single document.

When relevant and possible, data relating to a particular indication, dosage form, route of administration or dosing regimen should be presented in separate sections within the body of the PSUR and any safety concerns addressed accordingly without preparing a separate PSUR (e.g. a section dedicated on paediatric use summarising safety as well as exposure information).

In exceptional cases, SFDA or the MAH may consider it appropriate to have a separate PSUR. In such cases, agreement should be obtained at the time of authorisation or during the post-authorisation phase, as applicable. Examples include:

- Products authorised through line extensions to existing medicinal products (e.g. an active substance in two or more different formulations for systemic versus topical administration) with cross-reference between PSURs, if appropriate (see Chapter I.6, Section 2.4.c);
- Fixed combinations, where options include either a separate PSUR for the combination with cross-reference to the single-substance PSUR(s) or inclusion of the fixed combination data within one of the single-substance PSURs.

If a subsequent marketing authorisation is granted to a MAH for a product which contains the same active substance as one previously granted to the same MAH, the data lock points used for the PSURs for the first product should normally be used for the following joint PSURs covering the first and all subsequent products.

6.2.3. Products Authorised to More Than One MAH

Where a product is authorised to more than one MAH, in the case of multiple applications, submission of common PSURs is acceptable provided that the products remain identical in all respects apart from their invented names and that the PSURs are submitted separately by each MAH. The data lock point should be based on the birth date used for the first authorised product. The submission cover letter should confirm that the data in these PSURs are identical.

Generic products should preferably have the same PSUR submission periodicity as the Corresponding originator product (see Chapter I.6, Section 2.4.c). It is generally considered acceptable that MAHs for generic products collaborate on the preparation of PSURs. However, each MAH remains responsible for the appropriate submission of PSURs for their products. Where common PSURs are submitted, the MAHs should confirm in writing that the data in these PSURs are identical.
MAHs who have contractual arrangements in place but opt not to submit common PSURs, should ensure that all data which may meaningfully contribute to the safety analysis and influence any proposed or effected changes in the Product Information of the medicinal product authorised to the reporting MAH, should be included, with the source indicated, and discussed in the PSUR, even if it is known that they are included in another MAH’s PSUR.

6.2.4. Frequency of Review and Reporting

6.2.4.a. Regular and Ad Hoc Submission of Periodic Safety Update Reports

In accordance with the regular periodicity for PSUR submission, PSURs are required to be prepared and submitted:

- before initial placing on the Saudi market:
  - immediately upon request from SFDA; and
  - at least every 6 months after authorisation;
- after initial placing on Saudi market:
  - 6-monthly PSUR submissions should be continued until two full years of marketing experience in Saudi Arabia has been gained;
  - yearly PSURs for the following two years; and
  - thereafter PSURs should be submitted at 3-yearly intervals;
  - in addition, PSURs should be submitted immediately upon request from SFDA.

The first PSUR should have a data lock point within 6 months after granting of the marketing authorisation.

The date of initial placing on the Saudi market is the date of launch, for the first time.

Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the data lock point.

Because the renewal is an independent process, it does not change the data lock point and submission schedule for the PSURs. It should be noted that re-assessment of the risk-benefit balance at the time of renewal is an opportunity to review and, if necessary, change the periodicity PSUR, or to request a second renewal.

When yearly or 3-yearly PSURs are due for submission, multiple 6-monthly or yearly PSURs are acceptable, provided that the MAH submits a PSUR Summary Bridging Report, the content of which is described in Chapter I.6, Section 4. It should be noted that in such cases, the MAH should not send 6-monthly or yearly PSURs 60 days after the data lock points of these 6-monthly or yearly PSURs, but should send them only at the required due date (yearly or 3-yearly).

If a time gap occurs between the data lock point of a regular PSUR and a request from SFDA (e.g. renewal, Risk-Benefit Review, ad hoc PSUR request), a PSUR Addendum Report should also be submitted (see Chapter I.6, Section 5). For a PSUR that spans longer time intervals, e.g. 3 years, an Addendum Report would only be considered appropriate if the time since preparation of the 3-year PSUR and the locally required report is greater than 6 months.

For PSURs requested for immediate submission by SFDA on an ad hoc basis, the MAH should liaise with the SFDA to agree the PSUR submission date, depending on the urgency of the issue.

Exceptionally, a MAH may make a special request to the SFDA for 30 additional calendar days to submit a PSUR. Ideally, this request should be made before the data lock point. The SFDA should respond as rapidly as possible. The basis for such a request should be justified and could include:
• a large number of case reports for the reporting period, provided that there is no new significant safety concern;
• safety concerns raised by SFDA in the previous PSUR for which the MAH is preparing additional or further analysis in the next PSUR; and/or
• safety concerns identified by the MAH that might require additional or further analysis.

The MAH should make such a request only for the specific PSUR in question and not for subsequent PSURs. Subsequent PSURs will generally be expected to be submitted on the appropriate date in line with their original periodicity.

6.2.4.b. Submission of Periodic Safety Update Reports for Renewal of Marketing Authorisations

The MAH should submit safety data with the renewal application at least 6 months before the expiry date of the marketing authorisation in Saudi Arabia. For the submission of safety data as part of the application for renewal of the marketing authorisation, the PSUR concept should be used. The MAH should lock the data no more than 60 days before submitting the PSUR.

The data lock point for submission of safety information should be at 4 years and 4 months following the marketing authorisation date. Renewal applications may be submitted earlier than 6 months before the expiry date of the marketing authorisation.

For the purpose of the renewal application, the MAH should submit:

• the PSUR, or the PSUR plus a PSUR Addendum Report (see Chapter I.6, Section 5) or plus line-listings and/or summary tabulations, or only a PSUR Addendum Report, or only linelists and/or summary tabulations (see Chapter I.6, Sections 2.4.d and 2.6.c), covering the period since the data lock point of the last PSUR (e.g. for the first renewal, the safety data of this PSUR or Addendum Report together with the PSURs previously submitted should cover a period of 4 years and 4 months since the marketing authorisation); and

• a PSUR Summary Bridging Report, bridging all PSURs (including those already submitted) covering the period of 4 years and 4 months. Alternatively, the information which corresponds by its content with the PSUR Summary Bridging Report may be included in the Clinical Overview, to be submitted with the renewal application. It is accepted that previously submitted PSURs should not be re-submitted, provided that a list of original submission dates is appended to the Summary Bridging Report.

If at the time of the first renewal, the SFDA concludes that an additional renewal is needed, this conclusion may also include a requirement for an additional period of 6-monthly or yearly PSURs. The second renewal application should discuss PSURs data covering a five year period since the data lock point of the PSUR(s) submitted with the first renewal application.

Because the renewal is an independent process, it does not change the periodicity and submission dates for PSURs due as part of pharmacovigilance reporting requirements. It should be noted that reassessment of the risk-benefit balance at the time of renewal is an opportunity to review and, if necessary, change the PSUR periodicity, or to request a second renewal.

The MAH may discuss the requirements for PSURs for the renewal applications with the SFDA, and agree on the appropriate PSUR documentation required.
6.2.4.c. Circumstances Where the Periodicity May Be Amended

Submission of PSURs is part of the normal conditions of marketing authorisations and pharmacovigilance obligations of the MAH. The periodicity of PSUR submission may be amended, as required by SFDA or proposed by the MAH. This may result in more or less frequent submission of PSURs. However, submission of PSURs at a lower frequency than once every 3 years is not possible.

Where an amendment is proposed, the Applicant/MAH should submit, as part of the application for a marketing authorisation, a reasoned request for the amendment, which, if granted, becomes part of the conditions of authorisation. If a MAH applies for such an amendment following authorisation, such an application should follow the procedures for a type II variation.

Circumstances where less frequent submission of PSURs may be appropriate include:

- Products authorised through line-extensions to existing medicinal products;
- Newly authorised generic medicinal products.

A priori, a line-extension triggers the restart of the regular PSUR periodicity, unless a different periodicity has been agreed as a condition for the granting of the marketing authorization.

However, in many cases, there will be no need to restart the regular PSUR periodicity following the line-extension, as data for the newly authorised product may be addressed in the PSURs submitted according to the existing submission schedule. A justification for continuing the existing submission schedule should be provided by the MAH as part of the line-extension application, and the conditions for the authorisation will include any amendment of the periodicity, if required, as part of the outcome of the application evaluation.

Where separate PSURs for the product approved through the line-extension are considered appropriate, these should be submitted in accordance with the authorisation date of the newly approved product by starting the regular PSUR periodicity, while the PSUR submission for the previously authorised product(s) continues according to the existing submission schedule. These requirements should be reflected in the conditions for the authorisation. If/when separate PSURs are no longer considered necessary, data relevant to the product approved through the line-extension should be incorporated in a single PSUR covering all related products.

The addition of a paediatric indication for an existing medicinal product is an example of a line-extension which would result in re-starting the regular PSUR periodicity following the authorization date of the newly approved product (see Annex 3.1.3).

For newly authorised generic products or products authorised on the basis of informed consent applications, application for submission of PSURs on a 3-yearly basis may be included in the authorisation application. PSURs for such products should preferably have the same data lock points as the corresponding originator product (see Chapter I.6, Section 2.4.c). Such applications will be assessed on a case-by-case basis by the SFDA.

Circumstances where more frequent PSUR submission may be required include:

- variations introducing new indications, populations, dosage forms and routes of administrations;
- an active substance which is a different salt/ester or derivative (with the same therapeutic moiety);
- the presence of an excipient without an established safety profile; and
- a Risk Management Plan in place for a corresponding originator product requiring specific monitoring of a safety concern.
In some circumstances, e.g. for biological products, a change in the manufacturing process may require close monitoring of possible clinical impact in terms of safety. Therefore, the conditions under which the related variation of the marketing authorisation is granted, may include a re-start of the regular PSUR periodicity.

If the SFDA considers it appropriate to amend the PSUR periodicity and submission schedule, this should be clearly communicated to the MAH.

**6.2.4.d. Preparation of Periodic Safety Update Report according to the International Birth Dates**

medicinal products, which are also authorised outside Saudi Arabia, will have an International Birth Date (IBD).

The IBD is the date of first marketing authorisation of a medicinal product granted to the MAH (or a contractual partner of the MAH) anywhere in the world. For practical reasons, the IBD may be defined as the last day of the month in which this first authorisation date falls.

The Saudi Birth Date (SBD) is the date of first marketing authorisation granted for the medicinal product in Saudi Arabia to the MAH (see Glossary in Annex 1.1).

In order to harmonise PSUR submissions internationally, the MAH may use the IBD to determine the dates of the datalock points for the PSUR submission schedule, provided that the first datalock point falls within the 6 months following the SBD.

After initial placing of the product on the Saudi market, the MAH should submit at least four PSURs covering 6 months each, in order to ensure that two full years of experience with the product on the Saudi market are covered through provision of 6-monthly PSURs, while keeping the data lock point according to the IBD or SBD.

**6.2.5. Reference Safety Information**

An objective of a PSUR is to establish whether information recorded during the reporting period is in accordance with previous knowledge of the medicinal product’s safety, and to indicate whether changes should be made to the Product Information or the Risk Management Plan. Reference information is needed to carry out this comparison.

Having one reference safety document would facilitate a practical, efficient and consistent approach to the safety evaluation and make the PSUR a unique report also accepted in other regions of the world.

It is common practice for MAHs to prepare their own Company Core Data Sheet (CCDS), which includes material relating to safety, indications, dosing, pharmacology and other information concerning the product. A practical option for the purpose of the PSUR is for each MAH to use, as a reference, the safety information contained within the CCDS, which is referred to as Company Core Safety Information (CCSI).

For the purposes of PSURs, the CCSI forms the basis for determining whether an adverse reaction is already listed or is still unlisted (listed and unlisted are terms that are introduced to distinguish them from the usual terminology of expectedness, which is used in association with the authorised Product Information). The Summary of Product Characteristics (SPC) continues to be the reference document upon which expectedness is based for the purpose of expedited post-authorisation safety reporting in Saudi Arabia.
It is important to highlight meaningful differences between the CCSI and SPC in the cover letter accompanying the submission of the PSUR. The SPC should also be provided.

For 6-monthly and yearly PSURs the version of the CCSI in effect at the beginning of the period covered by the PSUR should be used as the reference information.

However, there may be valid reasons to use the CCSI in effect at the end of the period:

When producing a PSUR covering a period of more than one year or a PSUR Summary Bridging Report, it is often impractical to base the analysis of listedness on the CCSI that was in effect at the beginning of the period. There may be considerable variation in listedness over the reporting period. Therefore, the latest CCSI in effect at the end of the period may be used for PSURs covering a longer period. For PSURs covering a period of more than one year, when listedness is assessed at the time of PSUR preparation after the data lock point, it is generally considered appropriate to use the version of the CCSI in effect at the end of the reporting period as the reference document, as long as that choice is made clear in the PSUR.

Whether the CCSI valid at the beginning or at the end of the period covered in the PSUR is used, the MAH should ensure that all changes to the CCSI made over this period are described in the relevant section of the PSUR entitled “Changes to the Reference Safety Information” (see Chapter I.6, Section 3.5).

MAHs assessing listedness at case entry or on an ongoing basis throughout the reporting period should include the current version of the CCSI and comment on the reasons for any change in listedness assessment over time. In both cases, changes added since the previous PSUR should be explained in the PSUR sections “Changes to Reference Safety Information” (see Chapter I.6, Section 3.5) and/or “Overall Safety Evaluation” (see Chapter I.6, Section 3.10).

The Reference Safety Information to be used for PSURs for generic medicinal products based on SBD should consist of the common safety information that is included in all current SPCs of the concerned generic medicinal product, as authorised in Saudi Arabia at the time of the data lock point. In addition, a summary of the other safety information that was not included in all SPCs should be submitted. The MAH should indicate in the PSUR which changes to the Reference Safety Information as used are considered necessary on the basis of the data examined in the PSUR.

6.2.6. Presentation of Data on Individual Cases

6.2.6.a. Sources of Information

Generally, adverse reaction data from the following sources are potentially available to the MAH and should be included in the PSUR:

- Adverse reaction reports notified directly to the MAH (or through schemes under its control):
  - Spontaneous reports from Healthcare Professionals;
  - Reports from MAH-sponsored studies or named-patient/ compassionate use;
  - Reports from Patients and other Consumers (not medically confirmed).
- Literature
- Adverse reaction reports received from regulatory authorities worldwide:
  - Spontaneous and non-spontaneous reports from Healthcare Professionals;
  - Reports from Patients and other Consumers (not medically confirmed).
• Other sources of data including:
  • Exchange of reports on adverse reactions in the framework of contractual arrangements (e.g. licensors-licensees agreements);
  • Data from special registries;
  • Reports from poison control centres;
  • Epidemiological databases.

6.2.6.b. Description of the Adverse Reaction

The reaction terms used in the PSUR should be in accordance with the MedDRA terminology (see Annex 3.2.1).

Whenever possible, the original reporter’s reaction terms should be used to describe the adverse reaction. However, when the original reporter’s terms are not medically appropriate or meaningful, the MAH should use the best alternative compatible reaction terms from MedDRA to ensure the most accurate representation possible of the original terms. Under such circumstances, the following should be borne in mind:

• In order to be able to make it available on request, the “verbatim” information supplied by the original reporter should be kept on file (in the original language and/or as a medically valid English translation, if applicable).
• In the absence of a diagnosis by the original reporter, a suggested diagnosis for a symptom complex may be made by the MAH and used to describe the case, in addition to presenting the reported individual signs, symptoms and laboratory data.
• If the MAH disagrees with a diagnosis that is provided by the original reporter, such disagreement may be indicated within the line-listing of cases (see Chapter I.6, Section 2.6.c).
• The MAH should report and try to understand all information provided within a case report. An example is a laboratory abnormality not addressed/evaluated by the original reporter.

Therefore, when necessary and relevant, two descriptions of the signs, symptoms or diagnosis could be presented in the line-listing: first, the reaction as originally reported; second, when it differs, the MAH’s medical interpretation (identified by asterisk or other means).

6.2.6.c. Line listings and/or Summary Tabulations

Depending on their type or source, available adverse reaction cases should be presented as line-listings and/or as summary tabulations (see Table below).

A line-listing provides key information but not necessarily all the details customarily collected on individual cases; however, it does serve to help SFDA identify cases which they may wish to examine more completely by requesting full case reports.

The MAH should prepare line-listings of consistent structure and content for cases directly reported to him (or under his control), including those from persons and organisations with whom the MAH has set up contractual arrangements, as well as those received from worldwide regulatory authorities (see Chapter I.6, Section 2.6.a). They should usually do the same for published cases (usually well documented; if not, follow-up with the author may be possible). However, inclusion of individual cases from second- or third-hand sources, such as persons or organisations with whom the MAH has contractual arrangements and special registries (see Chapter I.6, Section 2.6.a) may not be possible without standardisation of data elements, or appropriate due to the paucity of information, and may represent unnecessary re-entry/re-processing of such information by the MAH. Therefore, summary tabulations or possibly a narrative review of these data are considered acceptable under these circumstances.
In addition to individual case line-listings, summary tabulations of adverse reaction terms for signs, symptoms and diagnoses across all patients should usually be presented to provide an overview. Such tabulations should be based on the data in the line-listings (e.g. all serious adverse reaction and all non-serious unlisted adverse reaction), and also on other cases for which line-listings are not requested (e.g. non-serious listed adverse reactions). Details are found in Chapter I.6, Sections 3.7.a and 3.7.b.

### Presentation of individual case histories in the PSUR:

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<th>Line-Listening Summary Tabulation</th>
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<td>- Regulatory authorities</td>
<td>serious</td>
<td>yes</td>
<td></td>
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<tr>
<td>- Contractual partners***</td>
<td>serious</td>
<td>yes</td>
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<tr>
<td>- Registries</td>
<td>serious</td>
<td>yes</td>
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<td>- Poison control centres</td>
<td>serious</td>
<td>yes</td>
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<tr>
<td>- Epidemiological databases</td>
<td>serious</td>
<td>yes</td>
<td></td>
</tr>
</tbody>
</table>

* Medically unconfirmed reports should be provided as an annex to the PSUR as a line-listing.
** Line-listing should be provided as an annex to the PSUR.
*** For the purpose of this Table, the term contractual partners does not refer to persons and organisations to whom the MAH has transferred pharmacovigilance tasks and functions. Such persons and organisations are included in “Direct Reports to MAH”.

### 6.3. Model for a Periodic Safety Update Report (PSUR)

The following Sections are organised as a model PSUR. In each of these Sections, guidance is provided on what should be included.

#### 6.3.1. PSUR section “Executive Summary”

The MAH should prepare a brief overview of each PSUR in the form of an Executive Summary to provide the reader with a description of the most important information. The Executive Summary should be placed at the beginning of the PSUR immediately after the title page and should include a summary of:

- The worldwide marketing authorisation status (including a list of countries where the product is authorised/marketeted and the authorised indications;
• Other relevant regulatory information related to the period covered by the PSUR (e.g. any urgent safety restriction should be highlighted);
• Exposure data (National & International)
• Number of new case reports received during the period covered by the PSUR and the cumulative numbers;
• Particular issues and safety concerns investigated;
• Overall findings of the PSUR;
• Conclusions.

When the MAH has performed a review of one or several specific safety concern(s), this should be stated in this Executive Summary (as well as the nature of safety concerns that have been reviewed).

6.3.2. PSUR section “Introduction”

The MAH should briefly introduce the product so that the PSUR “stands alone” but is also placed in perspective relative to previous PSURs and circumstances.

Reference should be made not only to product(s) covered by the PSUR but also those excluded.

Exclusions should be explained; for example, they may be covered in a separate PSUR (e.g. for a combination product).

If it is known that a PSUR on the same product(s) will be submitted by another Marketing Authorisation Holder and some of whose data are included in the PSUR (see Chapter I.6, Section 2.3), the possibility of data duplication should be noted.

6.3.3. PSUR section “Worldwide Marketing Authorisation Status”

This section of the PSUR provides cumulative information.

The following information should be provided for any indication, usually as a table, for all countries where a regulatory decision about marketing has been made related to the following:

• Dates of marketing authorisation and subsequent renewal (where PSURs are common for identical products with different invented names, or in the case of generic medicinal products, the list of the dates should cover all products separately);
• Any qualifications surrounding the authorisation, such as limits on indications if relevant to safety;
• Treatment indications and special populations covered by the market authorisation, when relevant;
• Lack of approval, including explanation, by worldwide regulatory authorities;
• Withdrawal by the company of an application for authorisation submission if related to safety or efficacy;
• Dates of launch (where PSURs are common for identical products with different invented names or in the case of generics, the listing of the dates should cover separately all products);
• Dates when the marketing authorisation has been revoked/withdrawn or dates when the marketing or marketing authorisation has been suspended either by a regulatory authority or voluntarily by the MAH;
• Invented name(s).

Typically, indications for use, populations treated (e.g. children vs. adults) and dosage forms will be the same in many or even most countries where the product is authorised. However, when there
are important differences, which would reflect different types of patient exposure, such information should be noted. This is especially true if there are meaningful differences in the newly reported safety information that are related to such different exposures.

If more convenient and useful, separate regulatory status tables for different product uses or forms should be utilised.

Country entries should be listed in chronological order of regulatory authorisations.

Annex 5.2.2 provides an example, with fictitious data for an antibiotic, of how such a table might be organised. The product was initially developed as a solid oral dosage form for out-patient treatment of various infections.

6.3.4. PSUR section “Update of Regulatory Authority or Marketing Authorisation Holder Actions taken for Safety Reasons”

This section should include details on the following types of worldwide actions relating to safety that were taken during the period covered by the PSUR and between data lock point and PSUR submission:

- Marketing authorisation withdrawal, revocation or suspension;
- Failure to obtain a marketing authorisation renewal;
- Restrictions on distribution;
- Clinical trial suspension;
- Dosage modification;
- Changes in target population or indications;
- Formulation changes;
- Urgent safety restrictions.

The safety-related reasons that led to these actions should be described and documentation appended when appropriate; any communication with Healthcare Professionals (e.g. Direct Healthcare Professional Communication (DHPC), commonly called “Dear Doctor Letter” (DDL)) as a result of such action should also be described with copies appended.

6.3.5. PSUR section “Changes to Reference Safety Information”

For 6-monthly and yearly PSURs, the version of the CCDS with its CCSI coming into effect at the beginning of the period covered by the report should normally be used as the reference information. For a PSUR covering a period of over one year, the latest CCSI in effect at the end of the period may be used (see Chapter I.6, Section 2.5).

The CCSI used as reference should be numbered, dated and appended to the PSUR and include the date of the last revision. Changes to the CCSI, such as new contraindications, precautions, warnings, adverse reactions or interactions, already made during the period covered by the PSUR, should be clearly described, with presentation of the modified sections. The revised CCSI should be used as the reference for the next PSUR and the next period (see also Chapter I.6, Section 2.5).

With the exception of emergency situations, it may take some time before intended modifications are introduced in the Product Information. Therefore, during that period the amended reference document (CCSI) may contain more “listed” information than the existing Product Information in many countries.
6.3.6. PSUR section “Patient Exposure”

Estimating patient exposure data for marketed medicinal products often relies on gross approximations of in-house or purchased sales data or volume to determine patient exposure. This is not always reliable or available for all products. For example, hospital-based (in-patient exposure) data from the major monitoring sources are frequently unavailable. It may also be difficult to obtain accurate data for medicinal products of which generic presentations are in use. For non-prescription products, use is often on an as-required basis, and individual packages are frequently used by multiple family members of different ages and weights.

Where possible, an estimate of patient exposure should cover the same period as the interim safety data. While it is recognised that it is usually difficult to obtain and validate accurate exposure data, an estimate of the number of patients exposed should be provided along with the method used to derive the estimate. An explanation and justification should be presented if the number of patients is impossible to estimate. In its place, other measures of exposure, such as patient-days, number of prescriptions or number of dosage units are considered appropriate; the method used should be explained. Given the difficulty of estimating cases, patient exposure should preferably be provided as person-time of exposure (days, months, years). The MAH should be consistent in its method of calculation across PSURs for the same product. If a change in the method is appropriate, then both methods and calculations should be shown in the PSUR introducing the change. If these or other more precise measures are not available, bulk sales (tonnage) may be used. The concept of a Defined Daily Dose may be used in arriving at patient exposure estimates. When possible and relevant, data broken down by sex and age (especially paediatric vs. adult) should be provided. Paediatric population exposure should be broken down according to age groups. An estimate of use outside the terms of the marketing authorisation should be provided along with the method used to provide the estimate. Pregnancy exposure should also be estimated specially in the case of pregnancy registries using the same data lock point as the PSUR.

When an observed pattern of case reports indicates a potential problem, details by country including Saudi Arabia (with locally recommended daily dose) or other breakdowns (e.g. indication, dosage form) should be presented if available.

When adverse reaction data from clinical studies are included in the PSUR, the relevant denominator(s) should be provided. For ongoing and/or blinded studies, an estimation of patient exposure may be made.

When exposure data are based on information from a period that does not fully cover the period of the PSUR, the MAH may extrapolate using the available data. If this is done it should be clearly indicated what data were used and why it is valid to extrapolate for the PSUR period in question (e.g. stable sales over a long period of time, seasonality of use of the product).

In a PSUR Summary Bridging Report, exposure should be presented including the full reporting period and explaining any differences in this estimation from the simple sum of exposure estimates included in the separate PSURs covered by the PSUR Summary Bridging Report. In addition, cumulative exposure estimates should be presented (for further guidance see explanations provided in the Risk Management Plan Template in Annex 5.1.1).
6.3.7. PSUR section “Presentation of Individual Case Histories”

This section should contain a description and analysis of selected cases containing new or relevant safety information and grouped preferably by medically relevant headings/MedDRA System Organ Classes (SOCs).

A description of the criteria used to select cases for presentation should be provided.

Follow-up data on individual cases may be obtained subsequent to their inclusion in a PSUR. If such information is relevant to the interpretation of the case (e.g. significant impact on the case description or analysis), the new information should be presented in the next PSUR, and the correction or clarification noted relative to the earlier case description. Cases where follow-up information is not considered to have any impact on the overall assessment of the case and has not led to relevant coding changes for the case, do not need to be discussed in the body text of the PSUR.

However, such cases should always be presented in cumulative tables and analyses if relevant.

With regard to the literature, MAHs should monitor standard, recognized medical and scientific journals for safety information relevant to their products and/or make use of one or more literature search/summary services for that purpose.

Published cases received from other sources (e.g. spontaneous reporting, studies) should only be included once and literature citation should be provided regardless of the “primary” source.

With regards to spontaneous reports that originate from Patients/Consumers, MAHs should:

- ensure review of data from Patients/Consumers or other non-healthcare professionals;
- include analysis of this data if associated with a safety concern in the PSUR section “Overall Safety Evaluation” (clearly identifying such reports by their source); and
- provide the data as a line-listing and summary tabulation (if considered appropriate).

6.3.7.a. “Cases Presented as Line-Listings”

The types of cases referenced below should be included in the line-listings. Attempts should be made to avoid duplicate reporting of cases from literature and regulatory sources.

- All serious adverse reactions and non-serious unlisted adverse reactions from spontaneous reporting;
- All serious adverse reactions (attributable to the medicinal product by either investigator or sponsor) available from post-authorisation safety studies (PASS) and other studies (including those which are part of the Risk Management Plan) or named patient/compassionate use;
- All serious adverse reactions, and non-serious unlisted adverse reactions from the literature;
- All serious adverse reactions transmitted to the MAH by worldwide regulatory authorities. In addition, the types of cases referenced below should be included as line-listings in the form of an annex to the PSUR:

- All non-serious listed adverse reactions from spontaneous reporting;
- All serious and non-serious (listed and unlisted) adverse reactions reported by Patients/Consumers and other non-healthcare professionals (not medically confirmed).

Suspected transmission via a medicinal product of any infectious agent should be considered as a serious adverse reaction (see Chapter I.5, Section 9).
Line-listing(s) (see Annex 5.2.3 for Template) should include each Patient only once regardless of how many adverse reaction terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed according to the most serious adverse reactions (sign, symptom or diagnosis), as judged by the MAH.

It is possible that the same Patient may experience different adverse reactions on different occasions (e.g. weeks apart during a clinical trial). Such experiences should be treated as separate reports. Under such circumstances, the same Patient might then be included in a line-listing more than once, and the line-listings should be cross-referenced when possible. Line-Listings should be organised (tabulated) by body system (MedDRA System Organ Classes (SOCs)).

Where common PSURs are submitted, the line-listings should still reflect the invented name of the medicinal product (or the active substance name if the invented name of the medicinal product is not available) as reported by the original reporter.

The following headings should usually be included in the line-listings (see Annex 5.2.3):

- MAH case reference number;
- Country in which the case occurred;
- Source (e.g. clinical trial, literature, spontaneous, regulatory authority);
- Age and sex of the Patient;
- Daily dose of the suspected medicinal product (and, when relevant, dosage form or route);
- Date of onset of the adverse reaction(s). If not available, best estimate of time to onset from therapy initiation. For adverse reactions known to occur after cessation of therapy, estimate of time lag if possible (may go in comments section);
- Dates of treatment. If not available, best estimate of treatment duration;
- Description of adverse reaction(s) as reported, and when necessary as interpreted by the MAH in English (see Chapter I.6, Section 2.6.b);
- Patient outcome (at case level) (e.g. resolved, fatal, improved, sequelae, unknown). This should indicate the consequences of the adverse reaction(s) for the Patient, using the worst of the different outcomes for multiple reactions;
- Comments, if relevant (e.g. causality assessment if the manufacturer disagrees with the reporter; concomitant medications suspected to play a role in the reactions directly or by interaction; indication treated with suspect medicinal product(s); dechallenge/rechallenge results if available). It should be used only for information that helps to clarify individual cases.

Depending on the product or circumstances, it may be useful or practical to have more than one line-listing, such as for different dosage forms or indications, if such differentiation facilitates presentation and interpretation of the data.

6.3.7.b. “Cases Presented as Summary Tabulations”

An aggregate summary for each of the line-listings should usually be presented. These tabulations usually contain more terms than patients. It would be useful to have separate tabulations (or columns) for serious reactions and for non-serious reactions, for listed and unlisted reactions; other breakdowns might also be appropriate (e.g. by source of report). See Annex 5.2.4 for a sample data presentation on serious reactions.

The terms used in these tables should ordinarily be those used by the MAH to describe the case (see Chapter I.6, Section 2.6.b).
Data on serious reactions from other sources (see Chapter I.6, Section 2.6.a) should normally be presented as a summary tabulation. If useful, the tabulations may, for example, be sorted by source of information or country.

When the number of cases is very small, or the information inadequate for any of the tabulations, a narrative description rather than a formal table is considered suitable.

As previously described, the data in summary tabulations should be interval data, as should the linelists from which they are derived. However, for adverse reactions that are both serious and unlisted, a cumulative figure (i.e. all cases reported to date) should be provided in the table(s) or as a narrative.

6.3.7.c. “MAH’s Analysis of Individual Case Histories”

This section may be used for brief comments on the data concerning individual cases. For example, discussion may be presented on particular serious or unanticipated findings (their nature, medical significance, mechanism, reporting frequency, etc.). The focus here should be on individual case discussion and should not be confused with the global assessment in the PSUR section “Overall Safety Evaluation” (see Chapter I.6, Section 3.10).

6.3.8. PSUR section “Studies”

All studies (non-clinical, clinical and epidemiological) yielding safety information (this includes lack of efficacy data) with a potential impact on product information, studies specifically planned, in progress and those published that address safety concerns should be included with a discussion of any interim or final results. The MAH should not routinely catalogue or describe all the studies. Studies that are part of the Risk Management Plan should be mentioned (see Chapter I.6, Section 3.9.c).

6.3.8.a. “Newly Analysed Studies”

All relevant studies containing important safety information and newly analysed during the reporting period should be described, including those from epidemiological, toxicological or laboratory investigations. Reference should be made to the Risk Management Plan, where applicable. The study design and results should be clearly and concisely presented with attention to the usual standards of data analysis and description that are applied to non-clinical and clinical study reports. Copies of full study reports should be appended, e.g. in case of post-authorisation safety studies and for other studies with a significant safety finding only if deemed appropriate.


New studies specifically planned or conducted to examine a safety concern (actual or hypothetical) should be described (e.g. objective, starting date, projected completion date, number of subjects, protocol abstract).

When possible and relevant, if an interim analysis was part of the study plan, the interim results of ongoing studies may be presented. When the study is completed and analysed, the final results should be presented in a subsequent PSUR as described in Chapter I.6, Section 3.8.a.

Copies of full reports should be appended in the case of post-authorisation safety studies and for other studies with a significant safety finding only if deemed appropriate.

Planned studies should be discussed in the Risk Management Plan (see Chapter I.3) and if relevant in the related PSUR section (see Chapter I.6, Section 3.9.c).
6.3.8.c. “Published Studies”

Reports in the scientific and medical literature, including relevant published abstracts from meetings, containing important safety findings (positive or negative) should be summarised and publication reference(s) provided.

6.3.8.d. “Other Studies”

The MAH should provide any relevant information from the data collected by pregnancy exposure registries and a discussion of the positive and negative experience of use of the medical product during pregnancy.

6.3.9. PSUR section “Other information”

6.3.9.a. “Efficacy-related Information”

For products used in prevention (e.g. vaccines) or in treatment of serious or life-threatening diseases (e.g. antibiotics and antiviral products) or products used in healthy Consumers (e.g. contraceptives), medically relevant lack of efficacy reports, which may represent a significant hazard, should be described and explained.

Where appropriate, all other medically relevant reports of lack of efficacy should be discussed in this section.

6.3.9.b. “Late-breaking Information”

Any important, new information received after the database was frozen for review and report preparation may be presented in this section. Examples include significant new cases or important follow-up data. These new data should be taken into account in the PSUR section “Overall Safety Evaluation” (see Chapter I.6, Section 3.10).

6.3.9.c. “Risk Management Plan”

When a specific Risk Management Plan is in place, it should be discussed. In this case, the status of the Risk Management Plan and its amendments prior to the data lock point should be presented together with all available study results.

The assessment of the effectiveness of the risk management system should be presented (see Chapter I.3).


When a more comprehensive safety or risk-benefit analysis (e.g. all indications reviewed) has been conducted separately, a summary of the analysis should be included in this section.

6.3.10. PSUR section “Overall Safety Evaluation”

The MAH should provide a concise analysis of the data presented, taking into account any late-breaking information (see Chapter I.6, Section 3.9.b), and followed by the MAH’s assessment of the significance of the data collected during the period. Discussion and analysis of the “Overall Safety Evaluation” should be organised by SOC rather than by listedness or seriousness; the latter properties should still be covered under each SOC. Although related terms may be found in different SOCs, they should be reviewed together for clinical relevance.
Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases (3).

The MAH should also review the cumulative experience and highlight any new information on:
- A change in characteristics of listed reactions, e.g. severity, outcome, target population;
- Serious unlisted adverse reactions, placing into perspective the cumulative reports;
- Non-serious unlisted adverse reactions;
- An increased reporting frequency of listed adverse reactions, including comments on whether it is believed the data reflect a meaningful change in adverse reactions occurrence.

This section should also explicitly address any new safety concern on the following (lack of significant new information should be mentioned for each):
- Interactions;
- Experience with overdose, deliberate or accidental, and its treatment;
- Abuse or misuse;
- Positive or negative experiences during pregnancy or lactation;
- Experience in special patient groups (e.g. children, elderly, organ impaired, a qualitative description of off-label use should be given);
- Effects of long-term treatment;
- Patient/Consumer and other non-healthcare professional reports (see Chapter I.6, Section 3.7), if appropriate;
- Prescription errors/medication errors, including those associated with invented names or with the presentation of the medicinal products, that have safety implications, if available.

A subsection of the PSUR should deal with use of the medicinal product in children if the product has a paediatric indication, if there is evidence of significant off-label use in children or if there are adverse reactions reported in the paediatric population. Data from completed or ongoing clinical trials should be presented separately from spontaneous reports (see Annex 3.1.3).

### 6.3.11. PSUR section “Conclusion”

The “Conclusion” should address the overall risk-benefit balance in the context of the data presented in the PSUR and:
- indicate which safety data are not in accordance with previous cumulative experience and the reference safety information (CCSI);
- specify and justify any action recommended or initiated.

The need to amend the SPC should be addressed in the cover letter from the MAH, where consistency between the CCSI and the SPC is cross-checked and any comment or planned action is proposed.

Having made a decision to amend the SPC, the MAH should submit a variation application at the same time as the PSUR or, where this is not possible, state a proposed timetable for submission.

### 6.4. Contents of the PSUR Summary Bridging Report

The PSUR Summary Bridging Report should not contain any new data but should provide a brief summary bridging two or more PSURs, or PSURs and PSUR Addendum Reports (e.g. two consecutive 6-monthly PSURs for a yearly PSUR or six consecutive 6-monthly PSURs to compile 3-year PSUR data). It is intended to assist SFDA with a helpful overview of the appended PSURs. The PSUR data should not be repeated but cross-referenced to individual PSURs. The format of the Summary
reactions ordered by SOC, seriousness and listedness covering the period of the Summary Bridging Report and pointing out any differences from prior listings or tabulations. In this case, there should be a clear understanding that the tables should be generated from live databases, which change over time as cases are updated. These tables should then reflect the most up-to-date data available at the time they are generated. It is recognised that the case counts in these summary tables may differ somewhat from the contents of the individual tables in the appended PSURs. A general statement describing the differences should Bridging Report should be identical to that of the usual PSUR, but the content should consist of summary highlights and an overview of data from the attached PSURs to which it refers.

A Summary Bridging Report should contain the following:

- Introduction (a brief description of the purpose of the document specifying the time periods covered and cross-referencing any appended PSURs);
- Worldwide marketing authorisation status (number of countries which have approved the product);
- Update on regulatory authority or MAH-initiated actions for safety reasons (an integrated summary of actions taken if appropriate);
- Changes to the CCSI (significant changes over the entire period);
- Exposure data (estimation of the total number of patients exposed in the time period);
- Individual case histories (brief statement outlining the total number of cases presented in the series of PSURs). When there is an important specific safety concern that has not been adequately discussed in one or more PSURs, it is considered appropriate to include a cumulative line-listing or summary tabulation for the types of cases of concern presenting adverse be provided);
- Studies (a brief summary of important targeted clinical safety studies);
- Other information (only highly significant safety information received after the data lock point);
- Overview of the safety concerns and Conclusion (unresolved key issues).

In addition, the cover letter accompanying the Summary Bridging Report should also contain information highlighting any significant differences between the approved SPC and the current CCSI.

6.5. Contents of the PSUR Addendum Report

A PSUR Addendum Report is an update to the most recently completed PSUR when a Competent Authority requests or requires a safety update outside the usual IBD-based PSUR submission schedule. An Addendum Report should be provided when more than 3 months for a 6-monthly or yearly PSUR, and more than 6 months for a PSUR covering a longer period have elapsed since the data lock point of the most recent PSUR. It may also be appropriate to provide an Addendum Report to the PSUR Summary Bridging Report (see Chapter I.6, Section 4).

The Addendum Report should summarise the safety data received between the data lock point of the most recent PSUR and the SFDA’s requested cut-off date. It is not intended that the Addendum Report should provide an in-depth analysis of the additional cases, as these should be included in the next regularly scheduled PSUR. Depending on the circumstances and the volume of additional data since the last scheduled report, an Addendum Report may follow the PSUR format or simplified presentation.

The proposed simplified presentation should include the following sections, containing any new information or changes beyond the most recent PSUR to which the Addendum Report refers:

- Introduction (purpose; cross-reference to most recent PSUR);
• Changes to the CCSI (including a copy of the most recent CCSI document if it differs from the one in the PSUR);
• Significant worldwide regulatory authorities’ actions relevant to safety;
• Line-listing(s) and/or summary tabulations;
• Conclusions (brief overview).
7. Company-Sponsored Post-Authorisation Safety Studies

7.1. Introduction

There is a continuous need to monitor the safety of medicinal products as they are used in clinical practice. Spontaneous reporting schemes provide important early signals of safety concerns and also provide a means of continuous surveillance. Formal studies to evaluate safety may also be necessary, particularly in the confirmation, characterisation and quantification of safety concerns identified at an earlier stage of product development or during post-authorisation use (see Chapter 1.8). Such studies may also be useful in identifying previously unsuspected adverse reactions or in confirming the safety profile of a medicinal product under normal conditions of use. In accordance with legal requirements, post-authorisation safety studies (PASS) may be required by Competent Authorities either as a commitment at the time of authorisation or in the post-authorisation phase to further assess a signal. In either case, such studies will be considered as a relevant part of the Risk Management Plan (see Chapter 1.3).

This Chapter applies to the conduct of studies sponsored by the pharmaceutical industry, which evaluate the safety of products with a marketing authorisation for human use. They encompass all studies carried out to evaluate the safety of authorised medicinal products and for which a MAH takes responsibility for their initiation, management and/or financing. This includes studies where the medicine is provided by the MAH and those where it is prescribed in the normal way, both in general practice and in the hospital setting. A study follows a protocol, which defines the study population and the design for its conduct and analysis. Therefore, in this context, databases searches to count e.g. number of adverse events or number of prescriptions are not considered studies.

The present guidance provides a framework whereby a variety of data collection methods may be used to evaluate the safety of authorised medicinal products. Whilst it is recognised that the study design used needs to be tailored to particular products and safety concerns, this guidance defines the essential principles to be applied in a variety of situations. The study methods in this field continue to develop and therefore there will be a need to regularly review guidance to ensure that it reflects advances made in the assessment of product safety (see Table I.7.A at the end of this Chapter).

A post-authorisation safety study is defined as “pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product”. The definition of non-interventional trial is: “A study where the medicinal product(s) is (are) 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 the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data”.

In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice. Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-authorisation safety studies. The latter are considered clinical trials.

If the definition of non-interventional is not met, the study should be considered as interventional. For instance, studies exploring new indications, new routes of administration or new combinations,
after a product has been authorised, should be considered as interventional. The guidance on Good Clinical Practice does not apply to non-interventional post-authorisation studies.

The guidance below relates principally to those non-interventional post-authorisation studies where there is a known safety issue under investigation and/or where the numbers of patients to be included in the study will add significantly to the existing safety data for the product(s).

A safety concern may be unexpectedly identified in the course of performing a study on an authorized medicinal product that would normally fall outside the scope of this guidance. In that case, the MAH and specifically the QPPV are expected to inform SFDA immediately and to provide a brief report on progress at intervals and at study end as requested by the SFDA.

If there is doubt as to whether or not a study comes under the scope of the present guidance, the company should discuss the intended protocol with SFDA(see Chapter I.7, Section 4.1).

In addition to the guidance below, MAHs should consider the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE) (1).

### 7.2. Objectives of Post-Authorisation Safety Studies

Post-authorisation safety studies may be conducted for the purpose of identifying previously unrecognised safety concerns (hypothesis-generation), investigating potential and identified risks (hypothesis-testing in order to substantiate a causal association), or confirming the known safety profile of a medicinal product under normal conditions of use. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Situations where studies may be appropriate include:

- a medicinal product with a novel chemical structure or novel mode of action;
- where there is uncertainty as to the clinical relevance of a toxic effect in animals;
- where there is uncertainty as to the safety profile;
- where there is a need to better quantify adverse events identified in clinical trials and elucidate risk factors;
- where there is a need to confirm or refute safety concerns suggested by other sources (e.g. spontaneous reporting);
- where there is a concern regarding the use of the medicinal product (e.g. to quantify the offlabel use); and
- when there is a need to evaluate the effectiveness of a risk minimisation measure.

A variety of designs may be appropriate including observational cohort studies, case-control studies or registries (see Table I.7.A). Clinical trials involving systematic allocation of treatment (e.g. randomisation) may also be used to evaluate the safety of authorised products.

The design to be used will depend on the objectives of the study, which must be clearly defined in the study protocol. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods. A reference to the Risk Management Plan should be made in the protocol when such a Plan exists.

For protocol development consideration should be given to the elements described in Table I.7.B at the end of this Chapter.
7.3. Responsibilities for the Conduct of Post-Authorisation Safety Studies

The MAH who initiates, manages and/or finances the study is responsible for its conduct and should meet the pharmacovigilance obligations concerning PASS. The study should be supervised by a designated monitor(s) or monitoring organisation and the names of the monitors should be recorded in the study documents. In case the MAH does not directly conduct the study, detailed and clear contractual agreements for meeting pharmacovigilance obligations should be documented (see Chapter I.1).

The QPPV should be involved in the review of protocols for all post-authorisation safety studies, in order to ensure compliance with pharmacovigilance requirements.

7.4. Liaison with SFDA

7.4.1. Evaluation of the Protocol

MAHs proposing to perform a post-authorisation safety study should send the protocol at an early stage to the SFDA. National legal requirements or guidelines should be taken into account where these exist.

a. Studies requested by SFDA

Before the study commences a protocol must be finalized which explains the aims and objectives of the study, the methods to be used (including statistical analysis and justification of sample size) and the record keeping which is to be maintained. The MAH should submit to the SFDA the protocol plus any proposed communications to doctors within one month of SFDA request and at least one month before the planned start of the study. The protocol should be approved by SFDA before the initiation of the study. When the MAH considers that the protocol requires major amendment, this should be reported to the SFDA who will consider its appropriateness and the need for further evaluation. Refinements of exposure and/or case definitions will normally not require notification.

b. Studies performed at MAH's initiative

When the study commenced, the MAH should inform the SFDA. Any major amendment to the protocol should be reported to the SFDA accompanied by a justification for it. Refinements of exposure and/or case definitions will normally not require notification.

7.4.2. Reporting of Adverse Reactions

For post-authorisation safety studies that qualify as clinical trials, the reporting requirements established for Periodic Safety Update Reports (PSURs) (see Chapter I.6) should be followed.

For non-interventional post-authorisation safety studies, conducted inside and outside Saudi Arabia, the usual regulatory requirements for reporting of adverse reactions should be fulfilled according to Chapters I.4. and I.6 (in conjunction with Part II for electronic exchange of Pharmacovigilance information).
This means that

- Reports of all serious adverse reactions arising from such studies within Saudi Arabia. should be reported on an expedited basis (i.e. within 15 days), to the SFDA. These reports should also be included in the PSURs (see Chapter I.6);
- Reports of all unexpected serious adverse reactions arising from such studies outside Saudi Arabia should be reported on an expedited basis to the SFDA. These reports should also be included in the PSURs (see Chapter I.6);
- Reports on expected serious adverse reactions occurring outside Saudi Arabia should be reported in accordance with Chapter I.6 on PSURs;

All adverse reactions/events including those which are considered non-serious, should be summarized in the final study report in frequency tables.

MAHs should ensure that they are notified by the investigator of serious adverse reactions and, if specified in the study protocol, of events (those not suspected by the investigator or the MAH to be adverse reactions).

In certain study designs, such as case-control or retrospective cohort studies (see Data Sources in Table I.7.A), in which it is not feasible or appropriate to make an assessment of causality between medical events recorded and the medicinal products at individual case level, expedited reporting of Individual Case Safety Reports (ICSRs) is not required. In case of doubt, the MAH should clarify the reporting requirements with SFDA.

7.4.3. Progress and Final Study Reports

a. Studies requested by SFDA

MAHs should provide a study progress report annually, or more frequently as requested by the SFDA (e.g. according to the Risk Management Plan milestones) or on their own initiative. If the study is discontinued, a final report should also be submitted, which will include the reasons for stopping the study.

The content of the progress report should follow a logical sequence and should include all the available data which is judged relevant for the progress of the study; e.g. number of patients who have entered the study according to their status (exposure, outcome, etc.), problems encountered and deviations from the expected plan. After review of the report, SFDA may request additional information.

A final study report should be submitted according to an agreed timetable (e.g. Risk Management Plan milestones). For the content of the final report consideration should be given to the recommendations laid down in Table I.7.C at the end of this Chapter. The findings of the study should be made public, preferably through scientific journals.

Both progress and final reports should be sent to the SFDA. For evaluation of such reports, the same procedure as for evaluation of the protocol should be followed (see Chapter I.7, Section 4.1).

b. Studies performed at MAH's initiative

Progress and final reports should be included or updated in the corresponding PSUR and/or Risk Management Plan. When a safety concern is raised, a report should be submitted immediately to the SFDA. The findings of the study should be made public, preferably through scientific journals.
7.5. **Promotion of Medicinal Products**

Post-authorisation studies should not be planned or conducted for the purposes of promoting the use of medicinal products.

Company sales and marketing representatives should not be involved in studies in such a way that it could be seen as a promotional exercise, such as in the recruitment of patients and physicians.

7.6. **Participation of Healthcare Professionals**

Subject to the Healthcare Professional’s terms of service, payment should be restricted to compensation of the Healthcare Professional for any additional time and expenses incurred.

No additional payment or inducement for a Healthcare Professional to participate in a post-authorisation safety study should be offered or given.

7.7. **Ethical Issues**

The highest possible standards of professional conduct and confidentiality must always be maintained and legislation on data protection followed. The Patient’s right to confidentiality is paramount. The Patient’s personal identifiers should be replaced by a code in the study documents, and only authorised persons should have access to identifiable personal details if data verification procedures demand inspection of such details. Responsibility for the retrieval of information from personal medical records lies with the Healthcare Professional(s) responsible for the Patient’s care. Such information from medical records should be provided to the MAH, who is thereafter responsible for the handling of such information.

It is recommended that non-interventional post-authorisation safety studies are referred to an Ethics Committee. Studies conducted entirely using records not containing any personal identifiers (e.g. anonymised records) may not require an ethical review of individual study protocols. National guidelines in this respect should be followed where they exist.

Explicit consent is required when the study plans to collect data containing personal identifiers, though some exceptions are envisaged.

7.8. **Procedure for Complaints**

A post-authorisation safety study, the objective, design or conduct of which gives cause for concern (e.g. using the study as a promotional activity), should be referred to the SFDA.
Spontaneous reporting schemes are valuable tools for providing safety signals in a continuous manner. In many situations, however, such passive surveillance should be complemented with more formal approaches in order to increase the sensitivity for risk identification or to confirm, characterise or quantify possible safety concerns. These more formal approaches are included under the term ‘post-authorisation safety studies’.

<table>
<thead>
<tr>
<th>TABLE I.7.A: EPIDEMIOLOGICAL METHODS FOR POST-AUTHORISATION SAFETY STUDIES</th>
</tr>
</thead>
</table>
| Spontaneous reporting schemes are valuable tools for providing safety signals in a continuous manner. In many situations, however, such passive surveillance should be complemented with more formal approaches in order to increase the sensitivity for risk identification or to confirm, characterise or quantify possible safety concerns. These more formal approaches are included under the term ‘post-authorisation safety studies’.

### 1. Study Designs

Post-authorisation safety studies may adopt different designs depending on their objectives. A brief description of the fundamental types of studies, as well as the types of data resources available, is provided hereafter. However, this table is not intended to be exhaustive and should be complemented with other widely available information sources (4-7). The ICH-E2E Guideline (see Annex 4) has been followed to a great extent in order to provide a harmonised view on this topic.

#### 1.1 Methods for 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 for later contact. 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.

##### 1.1.1 Sentinel Sites

Active surveillance 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. Active surveillance 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.

##### 1.1.2 Intensive Monitoring Schemes

Intensive monitoring is a system of record collection 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 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.
1.1.3 Prescription Event Monitoring

Prescription event monitoring is a method of active pharmacovigilance surveillance. 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 (8-9). Limitations of prescription event monitoring include incomplete physician response 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.

1.1.4 Registries

A registry is a list of patients presenting with the same characteristic(s). This characteristic may be a disease or an outcome (disease registry) or a specific exposure (exposure or drug registry). Both types of registries, which only differ by the type of patient data of interest, may collect a battery of information using standardised questionnaires in a prospective fashion. Disease/outcome registries, such as registries for blood dyscrasias, severe cutaneous reactions, or congenital malformations may help collect data on drug exposure and other factors associated with a clinical condition. A disease registry might also be used as a base for a case-control study comparing the drug exposure of cases identified from the registry and controls selected from either patients within the registry with another condition, or from outside the registry.

Exposure registries address populations exposed to medicinal products of interest (e.g. registry of rheumatoid arthritis patients exposed to biological therapies) to determine if a medicinal product has a special impact on this group of patients. Some exposure registries address exposures to medicinal products in specific populations, such as pregnant women. Patients may be followed over time and included in a cohort study to collect data on adverse events using standardized questionnaires. Single cohort studies may measure incidence, but, without a comparison group, cannot provide proof of association. However, 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 drug indicated for a specific condition.

1.2 Comparative 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 or case series. Major types of these designs are cross-sectional studies, case control studies, and cohort studies (both retrospective and prospective).

1.2.1 Cross-sectional Study (Survey)

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. The major drawback of cross-sectional studies is that the temporal relationship between exposure and outcome cannot be directly addressed, which limits its use for aetiologic 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.
### 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. Multiple adverse events may also be investigated using the same data source in a cohort 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 oversampling of these patients or by stratifying the cohort if sufficient numbers of patients exist. Cohort studies may be prospective or retrospective depending on when the outcome of interest occurs in relation to the commencement of the research: If the outcome occurs after the research begins, it would be prospective; if the outcome had already occurred when the investigation began, it would be retrospective.

### 1.2.3 Case-control Study

In a case-control study, cases of disease (or events) are identified. Controls, or patients without the disease or event of interest, are then selected from the source population that gave rise to the cases. The controls should be selected in such a way that the prevalence of exposure to the medicinal product among the controls represents the prevalence of exposure in the source population. The exposure status of the two groups is then compared using the odds ratio, which is an estimate of the relative risk of disease among the exposed as compared to the non-exposed. Patients may be identified from an existing database or using data collected specifically for the purpose of the study of interest. If safety information is sought for special populations, the cases and controls may be stratified according to the population of interest (the elderly, children, pregnant women, etc.). For rare adverse events, 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 risk factors for adverse events (or actually, effect-modifiers). Risk factors may include conditions such as renal and hepatic dysfunction, which might modify the relationship between the drug exposure and the adverse event. Under specific conditions, a case-control study may also provide the absolute incidence rate of the 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, an incidence rate can be calculated. As in cohort studies, case-control studies may be prospective or retrospective (see 1.2.2. of this Table). When the source population within which the case-control study is conducted is a well-defined cohort, it is then possible to select a random sample from it to form the control series. The name “nested case-control study” has been coined to designate those studies in which the control sampling is density-based (e.g. the control series represents the person-time distribution of exposure in the source population). The case-cohort is also a variant in which the control sampling is performed on those persons who make up the source population regardless of the duration of time they may have contributed to it (7). 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.
### 1.2.4 Other Novel Designs

Some novel designs have been described to assess the association between intermittent exposures and short-term events, including the case-series (10), the case-crossover (11) and the case-time-control (12) 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.

### 1.3 Clinical Trials

When significant risks are identified from pre-approval clinical trials, further clinical studies might be called for to evaluate the mechanism of action for the adverse reaction. In some instances, pharmacodynamic and pharmacokinetic studies might be conducted to determine whether a particular dosing instruction 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 general 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 drug concentration 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 the elderly, 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. In performing clinical trials, national legislative requirements or guidelines should be followed where these exist.

#### 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 absolute minimum consistent with the aims of the study (10). This design is best 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. These studies qualify as clinical trials and are subject to national legislative requirements or guidelines where these exist.

### 1.4 Other Studies

Descriptive studies are an important component of pharmacovigilance, although not for the detection or verification of adverse events associated with exposures to medicinal products. These studies are primarily used to obtain the background rate of outcome events and/or establish the prevalence of the use of medicinal products in specified populations.

#### 1.4.1 Occurrence of Disease

The science of epidemiology originally focused on the natural history of disease, including the characteristics of diseased patients and the distribution of disease in selected populations, as well as estimating the incidence and prevalence of potential outcomes of interest. These outcomes of interest now include a description of disease treatment patterns and adverse events. Studies that examine specific aspects of adverse events, such as the background incidence rate of or risk factors for the adverse event of interest, may be used to assist in putting spontaneous reports into perspective (4). For example, an epidemiologic study can be conducted using a disease registry to understand the frequency at which the event of interest might occur in specific subgroups, such as patients with concomitant illnesses.
### 1.4.2 Drug Utilisation Study

Drug utilisation studies (DUS) describe how a medicinal product is marketed, prescribed and used in a population, and how these factors influence outcomes, including clinical, social, and economic outcomes. These studies provide data on specific populations, such as the elderly, children, or patients with hepatic or renal dysfunction, often stratified by age, gender, concomitant medication and other characteristics. DUS may be used to determine if a product is being used in these populations. From these studies, denominator data may be derived for use in determining rates of adverse reactions. 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 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. Important limitations of these studies may include a lack of clinical outcome data or information of the indication for use of a product.

### 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. They 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. MAHs should select the best data source according to validity (e.g. completeness of relevant information, possibility of outcome validation) and efficiency criteria (e.g. time span to provide results). External validity should also be 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 MAH should evaluate the differences that may exist in the relevant variables (e.g. age, sex, pattern of use of the medicinal product) and the potential impact on the results. In the statistical analysis, the potential effect of modification of such variables should be explored.

With any data source used, the privacy and confidentiality regulations that apply to personal data should be followed.
**TABLE I.7.B: ELEMENTS TO BE CONSIDERED IN THE PROTOCOL OF POST-AUTHORISATION SAFETY STUDIES AS APPROPRIATE**

(Based on the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (1)).

<table>
<thead>
<tr>
<th>A</th>
<th>A descriptive title and version identifier (e.g. date)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>The names, titles, degrees, addresses and affiliations of all responsible parties, including the principal investigator, co-investigators and a list of all collaborating primary institutions and other relevant study sites</td>
</tr>
<tr>
<td>C</td>
<td>The name and address of the MAH</td>
</tr>
<tr>
<td>D</td>
<td>An abstract of the protocol</td>
</tr>
<tr>
<td>E</td>
<td>The proposed study tasks, milestones and timelines</td>
</tr>
<tr>
<td>F</td>
<td>A statement of research objectives, specific aims and rationale</td>
</tr>
</tbody>
</table>

Research objectives describe the knowledge or information to be gained from the study. Specific aims list the measurements to be made and any hypotheses to be tested. The protocol should distinguish between a priori research hypotheses and hypotheses that are generated based on knowledge of the source data. The rationale explains how achievement of the specific aims will further the research objectives.

| G | A critical review of the literature to evaluate pertinent information and gaps in knowledge |

The literature review should describe specific gaps in knowledge that the study is intended to fill. The literature review might encompass relevant animal and human experiments, clinical studies, vital statistics and previous epidemiologic studies. The literature review should also cite the findings of similar studies and the expected contribution of the current study.
A description of the research methods, including:

1. The overall research design, strategy and reasons for choosing the proposed study design
   *Research designs include case-control, cohort, cross-sectional, nested case-control or hybrid designs.*

2. The population or sample to be studied
   *The population is defined in terms of persons, place, time period and selection criteria. The rationale for the inclusion and exclusion criteria and their impact on the number of subjects available for analysis should be described. If any sampling from a base population is undertaken, details of sampling methods should be provided.*

3. The strategies and data sources for determining exposures, health outcomes and all other variables relevant to the study objectives, such as potential confounding variables and effect modifiers, using validated measurements whenever possible
   *Data sources might include questionnaires, hospital discharge files, abstracts of primary clinical records, administrative records such as eligibility files, prescription drug files, biological measurements, exposure/work history record reviews or exposure/disease registries.*

4. Clear operational definitions of health outcomes, exposures and other measured risk factors as well as selection criteria and comparison groups
   *An operational definition is one that can be implemented independently using the data available in the proposed study. For example, "PCP episode" is not an operational definition, whereas a better description would be "hospitalisation with a primary discharge diagnosis of ICD-9-CM code 136.3".*

5. Projected study size, statistical precision and the basis for their determination
   *Describe the relation between the specific aims of the study and the projected study size in relation to each outcome.*

6. Methods used in assembling the study data
   *This should include a description of or reference to any pre-testing procedures for research instruments and any manuals and formal training to be provided to interviewers, abstractors, coders or data entry personnel.*

7. Procedures for data management
   *Describe data management and statistical software programmes and hardware to be used in the study.*

8. Methods for data analysis
   *Data analysis includes all the major steps that lead from raw data to a final result, including methods used to correct inconsistencies or errors, to impute values or to modify raw data. Data analysis comprises comparisons and methods for analysing and presenting results, categorisations as well as procedures to control sources of bias and their influence on results, e.g. possible impact of biases due to selection, misclassification, confounding and missing data. The statistical procedures to be applied to the data to obtain point estimates and confidence intervals of measures of occurrence or effect, for instance, should be presented. Any sensitivity analyses undertaken should also be described.*

9. A description of quality assurance and quality control procedures for all phases of the study
   *Mechanisms to ensure data quality and integrity should be described, including, abstraction of original documents. As appropriate, include certification and/or qualifications of any supporting laboratory or research groups.*

10. Limitations of the study design, data sources and analytic methods
    *At a minimum, issues relating to confounding, misclassification, selection, generalisability and random error should be considered. The likely success of efforts taken to reduce errors should be discussed.*
<table>
<thead>
<tr>
<th></th>
<th>A description of plans for protecting human subjects</th>
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<tbody>
<tr>
<td><strong>I</strong></td>
<td>This section should include information about whether study subjects will be placed at risk as a result of the study, provisions for maintaining confidentiality of information on study subjects and potential circumstances and safeguards under which identifiable personal information may be provided to entities outside the study. Conditions under which the study would be terminated (stopping rules) should be described. Procedures for monitoring results should be described; for prospective studies consider using a Data Safety Monitoring Board (DSMB) for this purpose.</td>
</tr>
<tr>
<td></td>
<td>Management and reporting of adverse events/adverse reactions</td>
</tr>
<tr>
<td><strong>J</strong></td>
<td>This section should include the procedures for collecting, management and reporting of individual cases of adverse events or adverse reactions, as appropriate. If an exemption to the individual case reporting has been granted by the Competent Authorities, a mention should be made in this section along with a justification (the waiver must be attached as an annex).</td>
</tr>
<tr>
<td></td>
<td>A description of plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication</td>
</tr>
<tr>
<td><strong>K</strong></td>
<td>There is an ethical obligation to disseminate findings of potential scientific or public health importance (e.g. results pertaining to the safety of a marketed medicinal product).</td>
</tr>
<tr>
<td></td>
<td>Resources required to conduct the study</td>
</tr>
<tr>
<td><strong>L</strong></td>
<td>Describe time, personnel and equipment required to conduct the study, including a brief description of the role of each of the personnel assigned to the research project.</td>
</tr>
<tr>
<td></td>
<td>Bibliographic references</td>
</tr>
<tr>
<td><strong>M</strong></td>
<td>Bibliographic references</td>
</tr>
<tr>
<td></td>
<td>Dated amendments to the protocol</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>Significant deviations from the protocol, such as any changes in the population or sample that were implemented after the beginning of the study, should be documented in writing. Any changes made after data analysis has begun should be documented as such and the rationale provided.</td>
</tr>
<tr>
<td></td>
<td>Annexes</td>
</tr>
<tr>
<td><strong>O</strong></td>
<td>For any additional or complementary information on specific aspects not addressed in the body text (e.g. questionnaires, case report forms).</td>
</tr>
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</table>
**TABLE I.7.C: ELEMENTS TO BE CONSIDERED IN THE FINAL STUDY REPORT**

(Based on the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology(1)).

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>A descriptive title</td>
</tr>
<tr>
<td>2</td>
<td>An abstract</td>
</tr>
<tr>
<td>3</td>
<td>Purpose (objectives) of the research, as stated in the protocol</td>
</tr>
<tr>
<td>4</td>
<td>The names, titles, degrees, addresses and affiliations of the principal investigator and all co-investigators</td>
</tr>
<tr>
<td>5</td>
<td>Name and address of the MAH</td>
</tr>
<tr>
<td>6</td>
<td>Dates on which the study was initiated and completed</td>
</tr>
<tr>
<td>7</td>
<td>Introduction with background, purpose and specific aims of the study</td>
</tr>
<tr>
<td>8</td>
<td>A description of the research methods, including:</td>
</tr>
<tr>
<td></td>
<td>a) Source population and selection of study subjects;</td>
</tr>
<tr>
<td></td>
<td>b) Data collection methods and, if questionnaires or surveys are involved, complete copies (including skip patterns);</td>
</tr>
<tr>
<td></td>
<td>c) Transformations, calculations or operations on the data;</td>
</tr>
<tr>
<td></td>
<td>d) Statistical methods used in data analyses.</td>
</tr>
<tr>
<td>9</td>
<td>A description of circumstances that may have affected the quality or integrity of the data</td>
</tr>
<tr>
<td></td>
<td>Describe the limitations of study approach and the methods used to address them (e.g. response rates, missing or incomplete data).</td>
</tr>
<tr>
<td>10</td>
<td>Analysis of the data</td>
</tr>
<tr>
<td></td>
<td>Include sufficient tables, graphs and illustrations to present the pertinent data and to reflect the analyses performed.</td>
</tr>
<tr>
<td>11</td>
<td>Management and reporting of adverse events/adverse reactions</td>
</tr>
<tr>
<td>12</td>
<td>A statement of the conclusions drawn from the analyses of the data</td>
</tr>
<tr>
<td>13</td>
<td>A discussion of the implication of study results</td>
</tr>
<tr>
<td></td>
<td>Cite prior research in support of and in contrast to present findings. Discuss possible biases and limitations in present research.</td>
</tr>
</tbody>
</table>
8. Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action

8.1. Introduction

Granting of a marketing authorisation for a medicinal product indicates that it is considered to have a satisfactory risk-benefit balance under the conditions defined in the Summary of Product Characteristics (SPC) and in accordance with the Risk Management Plan (where applicable) (see Chapter I.3), on the basis of the information available at that time.

During the post-authorisation period, larger and more diverse populations than those during the development phase of the product are likely to be exposed. New information on the benefits and risks of the product will be generated, and evaluation of this information and any safety concerns should be an on-going process, both by the MAH and the SFDA.

Both the MAH and the SFDA must keep abreast of all relevant information in order to fulfil the following responsibilities:

- Ensuring that all sources of information are screened regularly to identify any potential signals;
- Ensuring that appropriate action is taken in response to new evidence which impacts on the known risk-benefit balance;
- Keeping the SFDA, Healthcare Professionals and Patients informed.

This Chapter

- outlines the responsibilities of MAHs in signal detection;
- provides the principles on which an assessment of the risk-benefit balance should be based; and
- outlines the steps that may be taken by MAHs in order to address a change in the risk-benefit balance.

8.2. Signal Detection and Evaluation

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. Standardised MedDRA Queries (SMQs) may be used for signal detection and the use of SMQs is recommended in order to retrieve and review cases of interest where signals are identified from adverse reaction databases (3). Rarely, even a single report of an unexpected adverse reaction may contain sufficient information to raise a signal on or establish a causal association with the suspected medicinal product and impact on the risk-benefit balance.

The responsibilities of the MAH, and in particular of the QPPV, are provided in Chapter I.1, Section 1. It is the responsibility of the QPPV to provide the SFDA with any information relevant to the evaluation of benefits and risks afforded by a medicinal product, including appropriate information on post-authorisation safety studies.

The MAH should immediately inform the SFDA of any prohibition or restriction imposed by the Competent/regulatory authorities of any country in the world in which the medicinal product is
marketed and of any other new information which might influence the evaluation of the benefits and risks of the medicinal product.

The MAH and the SFDA should agree on the appropriate scope and timelines for evaluation and agreed responsibilities for review. The MAH should provide a comprehensive evaluation of the issue and the risks in the context of the benefits at the earliest opportunity and no later than the agreed date specified in the written communications between the Competent Authority and the MAH.

8.3. Principles of Risk-Benefit Assessment

Overall risk-benefit assessment should take into account and balance all the benefits and risks referred to below. Risk-benefit assessment should be conducted separately in the context of each indication and population, which may impact on the conclusions and actions.

8.3.1. Assessment of Benefits

When a new or changing risk is identified, it is important to re-evaluate the benefit of the medicinal product using all available data. The benefit of a medicinal product can be seen as the decrease in disease burden associated with its use. Benefit is composed of many parameters including: the extent to which the medicinal product cures or improves the underlying condition or relieves the symptoms; the response rate and duration and quality of life. In the case of prophylactic medicinal products, the benefit may be considered as the reduction of the expected severity or incidence of the disease. With diagnostics, the benefit will be defined in terms of sensitivity and specificity or, in other words, false negative and false positive rates. Any available information on misuse of the product and on the level of compliance in clinical practice, which may have an impact on the evaluation of its benefits, should also be considered. The quality and degree of the evidence of benefit should be taken into account. Benefit should, as far as possible, be expressed in quantitative terms in a way that makes it comparable to the risks.

8.3.2. Assessment of Risks

Assessment of risk involves a stepwise process requiring identification, confirmation, characterization (including identification of risk factors), and quantification of the risk in the exposed population. Overall assessment of risk should consider all available sources of information, including:

- Spontaneous adverse reaction reports;
- Adverse reaction data from studies which may or may not be company-sponsored;
- In vitro and in vivo laboratory experiments;
- Epidemiological data (see Table I.7.A);
- Registries, for example of congenital anomaly/birth defects;
- Data published in the worldwide scientific literature or presented as abstracts, posters or communications;
- Investigations on Pharmaceutical quality, and
- Data on sales and product usage.

Important issues, which should be addressed in the assessment of adverse reactions, include evidence of causal association, seriousness, absolute and relative frequency and presence of risk factors, which may allow preventive measures. The quality and degree of evidence of risk should be taken into account. In the assessment of risks and consideration of regulatory action, it is important to note that rarely even a single case report may establish a causal association with the suspected medicinal product and impact on the risk-benefit balance. Risk assessment should also take account of the potential for overdose, misuse, abuse, off-label use and medication errors.
When new safety concerns are identified, which, could have an impact on the overall risk-benefit balance of a medicinal product, the MAH should propose appropriate studies to further investigate the nature and frequency of the adverse reactions. A new or updated Risk Management Plan should be proposed accordingly (see Chapter I.3). The studies should comply with the guidance provided in Chapter I.7.

### 8.3.3. Risk-Benefit Assessment

Whenever possible, both benefits and risks should be considered in absolute terms and in comparison to alternative treatments. The magnitude of risk that may be considered acceptable is dependent on the seriousness of disease being treated and on the efficacy of the medicinal product. For example:

- In the treatment of a disease with high mortality, a high risk of serious adverse reactions may be acceptable providing the benefits associated with treatment have been shown to be greater.
- For medicines used in chronic diseases or in prevention of disabling diseases, some level of risk may be acceptable if there is a substantial improvement in the prognosis or quality of life.
- In situations where the main benefit is symptom relief for minor illnesses in otherwise healthy individuals or where individuals are treated not only for their own benefit but also for the benefit of the community (e.g. vaccination), risk levels must be extremely low.
- In cases where therapeutic benefit is limited, even a few cases of a serious adverse reaction may suffice to render the risk-benefit balance as unfavourable.
- If, for two medicinal products with essentially similar efficacy and types of adverse reactions, one or more serious adverse reactions were shown to differ in frequency, the risk-benefit balance of the product with the higher adverse reaction frequency may no longer be acceptable.

The populations being treated must also be taken into account, as should off-label use.

### 8.4. Improving the Risk-Benefit Balance

The MAH should aim to optimise the safe use and the risk-benefit balance of an individual product and ensure that the adverse effects of a medicinal product do not exceed the benefits within the population treated. The risk-benefit balance of a medicinal product cannot be considered in isolation but should be compared with those of other treatments for the same disease.

The risk-benefit balance may be improved either by increasing the benefits (e.g. by restricting use to identified responders), or by reducing the risks by risk minimising measures (e.g. by contraindicating the use in patients particularly at risk, reducing dosage, introducing precautions of use and warnings and, if appropriate, pre-treatment tests to identify patients at risk, monitoring during treatment for early diagnosis of adverse reactions (see Table I.3.A for overview on risk minimisation methods). When proposing measures to improve the risk-benefit balance of a product, their feasibility in normal conditions of use should be taken into account. If dose reduction is considered as a method of risk minimisation, the impact of dose reduction on efficacy should be carefully evaluated.

The following types of action may be necessary and may be initiated by the MAH and/or by the SFDA:

- Variation of marketing authorisation(s) in respect of the indication, dosing recommendations, contraindications, warnings and precautions for use or information about adverse reactions or other sections of the SPC and the Package Leaflet (PL);
• Direct provision of important safety information to Healthcare Professionals and Patients/the public (e.g. through letters and/or bulletins or via electronic media) (see Chapter I.8, Section 6).

If there are important new safety concerns requiring urgent action, the MAH, should initiate an urgent safety restriction (USR) followed by a type II variation. These measures should be immediately communicated to the SFDA. If no objections are raised within 24 hours after receipt of an application, the USR may be introduced and the corresponding application for the variation should be submitted without delay to the SFDA.

8.5. Withdrawal of a Product from the Market on Risk-Benefit Grounds

In the event that the overall risk-benefit balance is considered to be unfavourable and proposed risk minimisation measures are considered inadequate to redress the balance, the medicinal product should be withdrawn from the market and Healthcare Professionals and Patients/the public should be informed as appropriate (see Chapter I.8, Section 6). Such action may be taken voluntarily by MAHs. It is recommended that any such intended measure be discussed at an early stage with SFDA. SFDA should be informed immediately of any definite action.

For reporting requirements for Individual Case Safety Reports following withdrawal of a marketing authorisation see Chapter I.5.

8.6. Communication

In the event of a product withdrawal, an urgent safety restriction or an important variation, the content of Public Statements, Direct Healthcare Professional Communication (DHPC) and other communication from the MAH to Healthcare Professionals, Patients and the general public, including the time frame for the distribution of such communication, should be agreed with the SFDA. MAHs are reminded of their legal obligations not to communicate information relating to pharmacovigilance concerns to the public without notification to the SFDA. For further guidance see Part III.
PART II

Guidelines for Marketing Authorisation Holders & SFDA on Electronic Exchange of Pharmacovigilance Information in Saudi Arabia
1. Introduction

Part II reflects the requirements for mandatory electronic reporting of adverse reactions, save in exceptional circumstances.

The mandatory electronic reporting of adverse reactions, save in exceptional circumstances, applies to all medicinal products authorised in Saudi Arabia. For further details reference should be made to Chapter I.2.

This chapter refers to the electronic exchange of pharmacovigilance information and provides a reference to the preparation and electronic transmission of Individual Case Safety Reports (ICSRs) for SFDA and MAHs in the Kingdom of Saudi Arabia.

The standards to support the electronic transmission of ICSRs on an expedited and periodic basis are defined in the frame of the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (referred to as ICH).

Taking into account the international dimension of adverse reaction reporting and the need to achieve uniformity and high quality with regard to content and format of ICSRs between all involved parties it is of utmost importance that all parties follow the applicable ICH and SFDA guidelines. This applies in particular to electronic reporting, which requires strict adherence to uniform standards.

Electronic reporting of ICSRs should be conducted by SFDA and MAHs.

To support the fulfillment of these electronic reporting obligations, SFDA established SaudiVigilance, the pharmacovigilance database and data-processing network with the following main objectives:

- Assist the rapid and secure transmission of ICSRs between SFDA and MAHs;
- Fully comply with the respective ICH and SFDA guidelines and standards as outlined in Chapter II.2;
- Facilitate the electronic reporting by providing the necessary technical tools to the SFDA and MAHs;
- Assist the administration and management of ICSRs;
- Provide signal detection functionalities and support scientific evaluation of ICSRs;
- Establish a central repository of highest quality data on electronically reported adverse reactions occurring within and outside Saudi Arabia.

2. Applicable Electronic Reporting Guidelines

The electronic transmission and management of ICSRs should be carried out by both SFDA & MAHs according to the following Guidelines and specifications:

- The ICH-E2A Guideline ‘Clinical Data Management: Definitions and the Standards for Expedited Reporting’, which presents the standard definitions and terminology for key aspects of clinical safety reporting and provides guidance on the appropriate mechanism for handling expedited reporting in the investigational phase (see Annex 4).
- The ICH-E2B(M) Guideline ‘Maintenance of the ICH guideline on clinical safety data management: data elements for transmission of Individual Case Safety Reports’ (recommended for adoption at Step 4 of the ICH Process on 17 July 1997 and amended for maintenance on 10 November 2000 by the ICH Steering Committee (including the Post-
Step 4 corrections agreed by the Steering Committee on 5 February 2001, (CPMP/ICH/287/95 modification corr.), which extends the above Guideline to standardise the data elements for the transmission of all types of ICSRs, regardless of their source and destination (see Annex 4).

- The ICH-E2C Guideline ‘Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs’ (CPMP/ICH/288/95) and its Addendum (CPMP/ICH/4679/02), which provides guidance on the format and content of safety updates, which need to be provided to regulatory authorities, at defined intervals, after the medicinal products have been authorized (see Annex 4).
- The ICH-E2D Guideline ‘Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting’ (November 2003, CPMP/ICH/3945/03), which provides further guidance on definitions and standards for post approval expedited reporting, as well as good case management practices (see Annex 4).
- The ICH-M1 Standard ‘Medical Dictionary for Regulatory Activities (MedDRA)’ in the latest version and related guidelines and Points-to-Consider Documents. The MedDRA terminology is designed to support the classification, retrieval, presentation and communication of medical information throughout the medicinal product regulatory life cycle (see Annex 4).
- The ICH-M2 Standard ‘Electronic Transmission of Individual Case Safety Reports Message Specification (ICH ICSR DTD Version 2.1)’ (CPMP/ICH/285/95 modification), which provides the standards for the safety messages, which can contain one or more ICSRs (see Annex 4).
- The ICH-M2 Recommendations (see Annex 4):
  - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) General Recommendation – ESTRI Gateway (10NOV2005)
  - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) Physical Media Recommendation – Floppy Disks (10NOV2005)
  - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) Physical Media Recommendation – CD-R 10NOV2005
  - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) Physical Media Recommendation – DVD RAM 10NOV2005
  - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) File Format Recommendation – PDF 10NOV2005
  - EWG M2 Recommendation to the ICH Steering Committee Electronic Standards for the Transfer of Regulatory Information (ESTRI) File Format Recommendation – XML 10NOV2005
- The ICH-M5 ‘Routes of Administration Controlled Vocabulary’ (CHMP/ICH/175860/2005), which provides standard terms for routes of administration (see Annex 4).
- The ICH-M5 ‘Units and Measurement Controlled Vocabulary’, (EMEA/CHMP/ICH/175818/2005), which provides standard terms for units and measurements (see Annex 4).
The Standard Terms on Pharmaceutical Dosage Forms as published by the Council of Europe as ‘Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers’ in the latest version.

The ‘Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance during the Pre and Post-authorisation Phase in the European Economic Area (EEA)’ (EMEA/115735/2004, adopted at EU level in September 2004, see Annex 3.1.1).

As technical standards are evolving over time, the above reference documents may require revision and maintenance. In this context, the latest version of these documents should always be taken into account.

For general terms and definitions reference should be made to the relevant chapters of the documents listed above.

3. Electronic Reporting of Individual Case Safety Reports and Definition of ‘Exceptional Circumstances’

The electronic reporting, save in exceptional circumstances, is mandatory for all authorised medicinal products in Saudi Arabia. Non-adherence to this requirement constitutes non-compliance with Saudi legislation as referred to in Chapter II.1.

‘Exceptional circumstances’ are defined as mechanical, program, electronic or communication failures that prevent electronic reporting of Individual Case Safety Reports (ICSRs) and medicinal product Reports (MPRs) in Pharmacovigilance during the Pre- and Post-authorisation Phase, see Annex 3.1.1).

Technical tools (SaudiVigilance) have been made available by the SFDA to interested MAH, to facilitate compliance with the electronic reporting requirements as defined in SFDA guideline.

4. Preparation of Individual Case Safety Reports and Data Privacy Laws

4.1. How to Prepare Individual Case Safety Reports

Medical and administrative data related to individual cases, which qualify for expedited and periodic reporting, should be provided in line with ICH-E2A, ICH-E2B(M), ICH-E2D, ICH-M1, ICH-M2. These data should be reported electronically in a fully structured format using all applicable and relevant E2B(M) data elements and standard terminologies. Any supporting information related to the individual case should be sufficiently described within an individual case safety report (ICSR) with reference to the documents that are held by the sender (ICH A.1.8.2: ‘List of documents held by sender’), which may need to be provided on request.

It is recognised that it is often difficult to obtain all details on a specific case. However, complete information for an individual case, that is available to the sender, should be reported in each ICSR. This applies to all types of ICSRs, i.e. reports with initial information on the case, follow-up information and cases highlighted for nullification (ICH-E2B(M) A.1.13: ‘Report nullification’ set to ‘yes’ and ICH- E2B(M) A.1.13.1: ‘Reason for nullification’ completed see also Chapter II.5 on nullification of individual cases).
In accordance with the international guideline on pharmacovigilance (ICH-E2D), a case narrative, i.e. a complete medical description of the case (ICH-E2B(M) B.5.1: ‘Case narrative including clinical course, therapeutic measures, outcome and additional relevant information’) should be provided at least for all serious cases. This case narrative should be a 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 including the outcome, relevant laboratory evidence (including normal ranges) and any other information that supports or refutes an adverse reaction. The narrative should serve as a comprehensive, stand-alone “medical report”. The information should be presented in a logical time sequence; ideally this should be presented in the chronology of the patient’s experience. Furthermore, the available information should be entered in structured format in the applicable ICH-E2B(M) fields, which should be repeated as necessary.

In follow-up reports, new information should be clearly identifiable in the case narrative section and provided in structured format in the applicable ICH-E2B(M) fields.

Abbreviations and acronyms should be avoided, with the possible exception of laboratory parameters and units.

Key information from supplementary records should be included in the report, and their availability should be mentioned in the narrative as well as in section ICH A.1.8.2: ‘List of documents held by sender’. Any relevant autopsy or post-mortem findings should also be summarised in the narrative and related documents should be provided according to national regulation and if allowed by the national data privacy laws.

An example of a standard narrative template is provided in CIOMS V(14).

In situations where it is unclear or evident that the sender has not transmitted the complete information available on the case in an ICSR in line with the instructions provided in this chapter, the receiver may request the sender to re-transmit the ICSR with the complete case information in electronic ICH-E2B(M) format as described in Chapter II.2 within 24 hours.

This should be seen in the light of qualitative signal detection and evaluation, where it is important for the receiver to have all available information on a case to perform the medical assessment.

The suspect, interacting and/or concomitant active substance(s)/invented name of the reported medicinal product(s) should be reported in accordance with the ICH-E2B(M) and as outlined in this Section. For combination medicinal products, which contain more than one active substance, each active substance needs to be reflected individually in section B.4.k.2.2 ‘Active substance name(s)’ of ICH-E2B(M), which needs to be repeated for each active substance contained in the combination product.

Where medicinal products cannot be described on the basis of the active substance(s) or the invented name, e.g. in case only the therapeutic class is reported by the primary source, or in case of other administered therapies that cannot be structured, this information should be reflected in section B.5.1 ‘Case narrative including clinical course, therapeutic measures, outcome and additional relevant information’.

4.2. How to Prepare Individual Case Safety Reports Related to Parent- Child/Foetus Cases

With regard to parent-child/ foetus cases, the following principles should be adhered to:

- In cases where a fetus or nursing infant is exposed to one or several medicinal products through the parent and experiences one or more adverse reactions/events, information on
both the parent and the child/fetus should be provided in the same report. Reports of these cases are referred to as parent-child/fetus reports.

- If there has been no reaction/event affecting the child/fetus, the parent-child/fetus report does not apply; i.e. the ICH-E2B(M) B.1 fields ‘Patients characteristics’ apply only to the parent (mother or father) who experienced the adverse reaction/event.

- For those cases describing miscarriage or fetal demise or early spontaneous abortion, only a parent report is applicable, i.e. ICH-E2B(M) B.1 fields ‘Patients characteristics’ apply to the mother. However, if suspect medicinal product(s) were taken by the father this information should be indicated in the section B.4.k.13 ‘Time intervals between drug administration and start of reaction/event’.

- If both the parent and the child/fetus sustain adverse reactions, two separate reports, i.e. one for the parent (mother or father) and one for the child/fetus, should be provided but they should be linked by using the ICH-E2B(M) field A.1.12 ‘Identification number of the report which is linked to this report’ in each report.

- If only the child/fetus has an adverse reaction/event (other than early spontaneous abortion/fetal demise) the information provided in this section applies only to the child/fetus, and characteristics concerning the parent (mother or father), who was the source of exposure to the suspect medicinal product should be provided in ICH-E2B(M) B.1.10 section ‘For a parent-child/fetus report, information concerning the parent’.

- If both parents are the source of the suspect drug(s) then the case should reflect the mother’s information in ICH-E2B(M) B.1.10 section ‘For a parent-child/fetus report, information concerning the parent’ and the case narrative (section B.5.1) should describe the entire case, including the father’s information.

### 4.3. How to Report Follow-up Information

ICSRs are sent at different times to multiple receivers. Therefore the initial/follow up status is independent upon the receiver. For this reason an item to capture follow-up status is not included in the ICH-E2B(M) data elements. However, the field ‘date of receipt of the most recent information for this report’ ICH-E2B(M) (A.1.7) taken together with the field ‘sender identifier’ ICH-E2B(M) (A.3.1.2) and the field ‘sender’s (case) report unique identifier’ ICH-E2B(M) (A.1.0.1) provide a mechanism for each receiver to identify whether the report being transmitted is an initial or follow-up report. For this reason these items are considered critical for each transmission. A precise date should be used (i.e. day, month, year).

This date should be changed each time follow up information is received by the sender.

New information should be clearly identifiable in the case narrative section and provided in structured format in the applicable ICH-E2B(M) fields.

The sender should report follow-up information on an expedited basis, if significant new medical information has been received. Significant new information relates e.g. to new adverse reaction(s), a change in the causality assessment and any new or updated information on the case that impacts on the medical interpretation of the case. Therefore, the identification of significant new information requiring expedited reporting always requires medical judgement.

Situations where the seriousness criteria and/or the causality assessment related to an individual case 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 be also considered as significant change and thus reported on an expedited basis.

In addition, the sender should also report follow-up information on an expedited basis, where new administrative information is available, that could impact on the case management e.g. new case identifiers have become known to the sender, which may have been used in previous transmissions (ICH-E2B(M) field A.1.11 ‘Other case identifiers in previous transmissions’); this information
may be specifically relevant for the receiver to manage potential duplicates. Another example refers to ICH-E2B(M) field A.1.8 ‘Additional available documents held by sender’, whereby new documents that have become available to the sender may be relevant for the medical assessment of the case.

In contrast, non-significant information, which does not impact on the medical evaluation of the case, does not require expedited reporting. This may refer for example to minor changes of dates (e.g. the day of the birth date) or corrections of typos in the previous case version. Naturally, medical judgment should be applied, as a change to the birth date may constitute a significant change (e.g. with implications on the age information of the patient).

In these situations where the case is amended without requiring expedited reporting, the date of receipt of the most recent information reported in the field ICH-E2B (M) A.1.7 ‘Date of receipt of the most recent information for this report’ should not be changed.

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, a change in the MedDRA coding due to a change in the interpretation of a previously reported adverse reaction may constitute a significant change and therefore should be reported on an expedited basis.

4.4. What to Take into Account for Data Privacy Laws

To comply with Saudi legislation on the protection of individuals with regard to the processing of personal data as referred to in Chapter I.7, Section 7, electronic transmission of ICSRs should operate on the principles of anonymised information, whereby the ICH guidelines should be adhered to as follows:

- ICH-E2B(M) field B.1.1 ‘Patient name or initials’:
  The information should be provided when it is in conformance with the confidentiality requirements. This also applies to medical record number(s) ICH-E2B (M) field (B.1.1.1). If the initials are known to the sender but cannot be transmitted due to data privacy requirements, this field should be populated with “PRIVACY”. If the initials of the patient are unknown to the sender, this field should be populated with “UNKNOWN”.

- ICH-E2B(M) field B1.2.1 ‘Patient birth date’, ICH-E2B(M) field B.1.2.2 ‘Patient age at the time of the onset of reaction/event’ or ICH-E2B(M) field B.1.2.3 ‘Patient age group’:
  Only one of the elements describing age should be used. The choice should be based upon the most precise information available and in conformance with the national confidentiality requirements.

- Narratives in ICH-E2B(M)
  When information on individuals is reflected in narratives (e.g. ICH-E2B(M) section B.1.7 ‘Relevant medical history and concurrent conditions’ ICH-E2B(M) section B.1.10.7 ‘Relevant medical history and concurrent conditions of parent’ ICH-E2B(M) section B.5 ‘Narrative case summary and further information’), it should be provided in such a way that it can support the case evaluation and assessment by the receiver, but does not allow for the identification of the individual concerned. Taking the example of age, no date of birth should be provided but the age or age group in accordance with national confidentiality requirements.
5. Nullification of Individual Cases

In line with the ICH-E2B(M) 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 number (ICH-E2B(M) field A.1.0.1 ‘Sender’s (case) safety report unique identifier’ and ICH-E2B(M) field A.1.10 ‘Worldwide unique case identification number’) previously submitted. A nullified case is one that should no longer be considered for scientific evaluation.

When nullifying a case the following principles need to be taken into account:

- The flag ICH-E2B(M) field A.1.13 ‘Report nullification’ should be set to ‘Yes’ and the nullification reason should be provided in the field ICH-E2B(M) field A.1.13.1 ‘Reason for nullification’. The nullification reason should be clear and concise to explain why this report 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 ICH-E2B(M) A.1.0.1 ‘Sender’s (case) safety report unique identifier’ and ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ should be assigned.
- Individual versions of ICSRs cannot be nullified, only the individual case to which they refer.
- 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 report. The duplicate number fields in this report ICH-E2B(M) field A.1.11.1 ‘Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)’ and ICH-E2B(M) field A.1.11.2 ‘Case identifier(s)’ should be updated with the case identification numbers of the nullified case.

The Table below gives examples for different scenarios for which nullifications should and should not be carried out. It will also provide information on what to do in specific situations.
<table>
<thead>
<tr>
<th>Ex.</th>
<th>Scenario</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>An individual case has been identified as a duplicate of another individual case previously submitted.</td>
<td>One of the individual cases should be nullified. The remaining valid case should be updated with any additional information as relevant to the nullified case. The update of the remaining case should be performed in form of a follow-up report. The duplicate number fields in this report ICH-E2B(M) A.1.11.1 ‘Source(s) of the case identifier (e.g. name of the company, name of regulatory agency)’ and ICH-E2B(M) A.1.11.2 ‘Case identifier(s)’ should be updated with the case identification numbers of the nullified case.</td>
</tr>
<tr>
<td>2</td>
<td>A wrong ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ was accidentally used. This wrong ICH-E2B(M) A.1.10 Worldwide unique case identification number did not refer to any existing case.</td>
<td>The report with the wrong ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ should be nullified. A new case should be created based on an ICSR with the correct ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’.</td>
</tr>
<tr>
<td>3</td>
<td>On receipt of further information it is confirmed that the adverse reaction occurred before the suspect drug(s) was taken.</td>
<td>The case should be nullified.</td>
</tr>
<tr>
<td>4</td>
<td>On receipt of further information on an individual case, it is confirmed that the patient did not receive the suspect drug and the minimum reporting criteria for an ICSR as outlined in the ICH-E2B(M) guideline are no longer met.</td>
<td>The case should be nullified.</td>
</tr>
<tr>
<td>5</td>
<td>On receipt of further information it is confirmed that the reported adverse reaction(s) did not occur to the patient.</td>
<td>The case should be nullified.</td>
</tr>
<tr>
<td>6</td>
<td>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 the ICH-E2B(M) guideline are no longer met.</td>
<td>If it is not possible to obtain confirmation of the patient’s existence, then the case should be nullified.</td>
</tr>
<tr>
<td>Ex.</td>
<td>Scenario</td>
<td>Action</td>
</tr>
<tr>
<td>-----</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>7</td>
<td>A wrong ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ was accidentally used. This wrong ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ referred to an existing case.</td>
<td>The report with the wrong ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ should not be nullified. A follow-up report should be created to correct the information previously submitted. A new ICSR should be created and submitted with the correct ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’.</td>
</tr>
<tr>
<td>8</td>
<td>On receipt of further information on an individual case, it is confirmed that the patient did not receive the MAH’s suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for an ICSR as outlined in the ICH-E2B(M) guideline are still met.</td>
<td>The case should not be nullified.</td>
</tr>
<tr>
<td>9</td>
<td>On receipt of further information it is confirmed that the individual case was not medically confirmed.</td>
<td>The case should not be nullified. A follow-up report should be submitted within the appropriate timeframe with the primary source information updated: The field ICH-E2B(M) A.2.1.4 ‘Qualification’ should be set to ‘Consumer or other non health professional’ or ‘Lawyer’ as applicable; the field ICH-E2B(M) A.1.14 ‘Was the case medically confirmed, if not initially from a health professional?’ should be set to ‘No’.</td>
</tr>
<tr>
<td>10</td>
<td>On receipt of further information the reporter has confirmed that the reported adverse reaction is no longer considered to be related to the suspect drug(s).</td>
<td>The case should not be nullified. A follow-up report should be submitted within the appropriate timeframe with the updated information on the case.</td>
</tr>
<tr>
<td>11</td>
<td>Change of the individual case from serious to non-serious (downgrading).</td>
<td>The case should not be nullified. A follow-up report should be submitted with the seriousness flags ICH-E2B(M) field A.1.5.1 ‘Seriousness’ set to ‘No’ without selection of a value for the ICH-E2B(M) field A.1.5.2 ‘Seriousness criteria’. The flag ICH-E2B(M) field A.1.9 ‘Does this case fulfil the local criteria for an expedited report?’ should also be set to ‘No’.</td>
</tr>
<tr>
<td>12</td>
<td>The reported adverse reaction was considered to be a post-study event (it occurred outside of the study period, including follow-up period).</td>
<td>The case should not be nullified. If the adverse reaction is no longer reportable under the terms of an investigational clinical trial, a new case should be created and submitted with the appropriate report type selected for the field ICH-E2B(M) A.1.4 ‘Type of report’.</td>
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</tr>
<tr>
<td>13</td>
<td>The drug taken belongs to another MAH (e.g. a product with the same active substance but marketed under a different invented name).</td>
<td>The case should not be nullified. It is recommended that the initial sender informs the other MAH about this case (including the ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’ used). The original organisation should also submit a follow-up report to provide this new information. The other concerned MAH should create a new case and specify in the fields ICH-E2B(M) A.1.11.1 ‘Source(s) of the case identifier (e.g. name of the company name of regulatory agency)’ and ICH-E2B(M) A.1.11.2 ‘Case identifier(s)’ the reference case number and the name of the initial sending MAH.</td>
</tr>
<tr>
<td>14</td>
<td>The suspect drug taken does not belong to the MAH (same active substance, the invented name is unknown and the report originates from a country, where the MAH has no marketing authorisation for the medicinal product in question).</td>
<td>The case should not be nullified. The MAH should submit a follow-up report with this information (see Chapter I.4)</td>
</tr>
<tr>
<td>15</td>
<td>The case is mistakenly reported by MAH A although MAH B as co-marketer is responsible for reporting the case.</td>
<td>The case should not be nullified. An explanation should be sent by the MAH A to the co-marketer MAH B that the case has already been reported. The MAH B should provide any additional information on the case as a follow-up report with the same ICH-E2B(M) A.1.10 ‘Worldwide unique case identification number’.</td>
</tr>
</tbody>
</table>
6. Handling of Adverse Reaction Reports Published in the Worldwide Literature

General requirements in relation to adverse reaction reports published in the worldwide literature are described in Chapter I.4, Section 3.2.

When reports from the world-wide literature are submitted as ICSRs, the literature references should be provided in the Vancouver Convention (known as “Vancouver style”) as developed by the International Committee of Medical Journal Editors in the field ICH-E2B(M) A.2.2 ‘Literature reference(s)’. The standard format as well as those for special situations can be found in the following reference, which is in the Vancouver style (15).

For initial reporting of a case described in the literature in the form of an ICSR, a summary of the case in English (English abstract of the literature article) is regarded as sufficient to meet the expedited reporting criteria. This case summary should be provided in the field ICH-E2B(M) B.5.1 ‘Case narrative including clinical course, therapeutic measures’.

If considered necessary, SFDA may request a full translation of the copy of the literature article from the sender.

In addition to the ICSR, a copy of the literature article should be provided. Until standards for the electronic transmission of attachments (e.g. copies of literature articles) are developed in the frame of ICH, the sender should follow the rules outlined below:

- Mailing address and format of literature articles:
  - Literature articles reportable to the SFDA should be provided in PDF format and sent via email to the following e-mail address: npc.drug@sfda.gov.sa.

- 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(M) 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(M) 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.

  Example:
  ICSR: FR-ORGABC-23232321 (ICH-E2B(M) field A.1.10.1 World-Wide Unique Case Identification Number);
  Follow-up information published in the literature in a separate article:
  ICSR: FR-ORGABC-23232321 (ICH-E2B(M) field A.1.10.1 World-Wide Unique Case Identification Number remains unchanged);

- Reporting of cases reported in the worldwide literature referring to more than one patient:
  When the worldwide 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’ (ICH-E2B(M) field 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 section ICH-E2B(M) field A.1.12 ‘Identification number of the report.
which is linked to this report’ and the section should be repeated as necessary to cross refer all related cases.
See Table below for an example for the reporting of cases reported in the worldwide literature referring to more than one patient.

**TABLE II.6.A: EXAMPLE FOR THE REPORTING OF CASES ORIGINALLY REPORTED IN THE WORLDWIDE LITERATURE REFERRING TO MORE THAN ONE PATIENT**

<table>
<thead>
<tr>
<th>Example</th>
<th>Action</th>
</tr>
</thead>
</table>
| A literature article describes serious adverse reactions that have been experienced by 3 patients. For this scenario 3 ICSRs should be submitted, reporting for each individual patient the adverse reactions and all other available information on the case. | For Case 1 described in the literature article:  
- ICH-E2B(M) A.1.10.1 ‘World-Wide Unique Case Identification Number’:
  UK-ORGABC-0001  
- ICH-E2B(M) A.1.12 Linked Report:
  UK-ORGABC-0002  
- ICH-E2B(M) A.1.12 Linked Report:
  UK-ORGABC-0003  
- ICH-E2B(M) A.2.2 ‘Literature reference(s):’
  Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals:
  File name for the copy of literature article to be sent via e-mail to npc.drug@sFDA.gov.sa:
  UK-ORGABC-0001.pdf  
For Case 2 described in the literature article:  
- ICH-E2B(M) A.1.10.1 ‘World-Wide Unique Case Identification Number’:
  UK-ORGABC-0002  
- ICH-E2B(M) A.1.12 Linked Report:
  UK-ORGABC-0001  
- ICH-E2B(M) A.1.12 Linked Report:
  UK-ORGABC-0003  
- ICH-E2B(M) A.2.2 ‘Literature reference(s):’
  Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals:
  No copy of the literature article required since the copy was already submitted for case1.  
For Case 3 described in the literature article:  
- ICH-E2B(M) A.1.10.1 ‘World-Wide Unique Case Identification Number’:
  UK-ORGABC-0003  
- ICH-E2B(M) A.1.12 Linked Report:
  UK-ORGABC-0001  
- ICH-E2B(M) A.1.12 Linked Report:
  UK-ORGABC-0002  
- ICH E2B(M) A.2.2 ‘Literature reference(s):’
  Literature reference in line with uniform requirements for manuscripts submitted to biomedical journals:
  No copy of the literature article required since the copy was already submitted for case1. |
7. Compliance with Required Reporting Timeframes

MAHs and SFDA should ensure that the timeframes regarding the expedited reporting requirements as defined in Chapter I.4, Section 2 are adhered to.

8. Electronic Reporting through Company’s Headquarters

The MAH’s QPPV should ensure that all ICSRs are submitted electronically to the SFDA. If a pharmaceutical company decides to centralise the electronic reporting of the ICSRs (e.g. reporting through the company’s headquarters), it is the MAH’s (e.g. the local affiliate) responsibility to ensure that ICSRs are submitted electronically to the SFDA as applicable.

The following should be taken into account:

- The arrangement should be clearly specified in the MAH’s internal Standard Operating Procedures (SOPs).
- The SFDA should be notified in writing about the arrangement.
- The MAH should be registered with SaudiVigilance.
- Whoever is the physical sender of the electronic ICSRs, the MAH (i.e. local affiliate) will remain the contact point for all pharmacovigilance-related matters and responsible for the compliance with the pharmacovigilance obligations as defined in this guideline.

9. Data Quality of Individual Case Safety Reports Transmitted Electronically

SaudiVigilance should contain all reports of adverse reactions reportable according to Saudi guideline to support pharmacovigilance and Risk Management activities. This applies to all authorized medicinal products.

In addition, SaudiVigilance should be based on the highest internationally recognised data quality standards. To achieve these objectives, SFDA and MAHs should fully adhere to:

- The electronic reporting requirements as defined in this guideline;
- The concepts of data structuring, coding and reporting in line with the guidelines and standards referred to in this Chapter.

This is a pre-requisite to establish a properly functioning Saudi pharmacovigilance system (SaudiVigilance) intended to support the Saudi Risk Management activities.

10. Reporting of all Serious Cases from outside Saudi Arabia

The MAH is required to report all suspected serious unexpected adverse reactions that occur in third countries on an expedited basis to the SFDA.

To facilitate the overall reporting process to the SFDA, MAHs are encouraged to report electronically to SaudiVigilance all suspected serious adverse reactions that occur in a third country, for all medicinal products authorised in Saudi Arabia.
PART III

Guidelines for Marketing Authorisation Holders and Competent Authorities on Pharmacovigilance Communication
1. Direct Healthcare Professional Communications

1.1. Introduction

The aim of this guidance is to establish principles for the content and format of Direct Healthcare Professional Communications (DHPCs) (commonly called “Dear Doctor-letters” (DDL)), as well as describing situations where dissemination of DHPCs should be considered. The guidance also aims to describe the main requirements and procedures for such communications on the safe and effective use of medicinal products for human use. DHPCs relating to quality defects with medicinal products are outside the scope of this guidance.

As part of the risk management process (see Chapter I.3), SFDA will communicate to the public and healthcare professional on matters relating to pharmacovigilance and the safe use of medicinal products.

1.2. Definition of Direct Healthcare Professional Communication

A Direct Healthcare Professional Communication (DHPC) is defined as information aimed at ensuring safe and effective use of medicinal products which is delivered directly to individual Healthcare Professionals by a MAH, or by SFDA (this excludes direct personal replies to requests from individual Healthcare Professionals). Such DHPCs should not include any material or statement which might constitute advertising, or which is considered to be promotional or commercial by the SFDA.

1.3. Key Principles for Public Communication on Medicinal Products

The following key principles should be considered for public communication on medicinal products in general and by means of DHPCs in particular:

- Provision of information about the safe and effective use of medicinal products supports appropriate use and should be considered as a public health responsibility.
- Communication of such information needs to be considered throughout the risk management process (see Chapter I.3).
- It is essential that such information is communicated to Healthcare Professionals and relevant partners including Patient and Healthcare Professional organisations, societies and pharmaceutical wholesalers.
- In principle, significant new or emerging information should be brought to the attention of Healthcare Professionals before the general public, in order to enable them to take action and respond to Patients adequately and promptly. The important function of Healthcare Professionals in disseminating such information to Patients and the general public is recognised and should be supported.
- The overriding principle should be to ensure that the right message is delivered to the right persons at the right time.
- Effective communication on safe and effective use of medicinal products authorised in Saudi Arabia entails:
  - co-operation of all partners;
  - co-ordination between relevant partners, within and, if possible, outside the Saudi Arabia; and
• a strategy which meets the requirements resulting from the urgency to communicate and the expected public health impact of the information.
• A DHPC should not usually be distributed before the corresponding regulatory procedure has been completed, however, exceptionally (e.g. in the case of an urgent safety restriction) there may be a need to disseminate a DHPC prior to completion of a procedure.
• In general, an agreement between the MAH and SFDA is needed on the format and content of the information, recipients and the timetable. The agreed timetable for release of the information should be fully respected by all partners.

1.4. Situations Where a Direct Healthcare Professional Communication Should Be Considered

Dissemination of a DHPC is usually required in the following situations:

• Suspension, withdrawal or revocation of a marketing authorisation with recall of the medicinal product from the market for safety reasons; or
• Important changes to the Summary of Product Characteristics (SPC), for instance those introduced by means of an urgent safety restriction (e.g. introduction of new contraindications, warnings, reduction in the recommended dose, restriction of the indications, restriction in the availability of the medicinal product); or
• Completion of a referral procedure triggered for safety concerns which results in a significant change to the product information; or
• In other situations relevant to the safe and effective use of the medicinal product at the request of SFDA.

Other situations where dissemination of a DHPC may be appropriate include:

• A change in the outcome of the evaluation of the risk-benefit balance due to:
  • new data, in particular from a study or spontaneous reports that identify a previously unknown risk or a change in the frequency or severity of a known risk; or
  • new data on risk factors and/or on how adverse reactions may be prevented; or
  • substantiated knowledge that the medicinal product is not as effective as previously considered; or
  • evidence that the risks of a particular product are greater than those of alternatives with similar efficacy; or
• Availability of new recommendations for treating adverse reactions; or
• Ongoing assessment of a possible significant risk, but insufficient data at a particular point in time to take any regulatory action (in this case, the DHCP should encourage close monitoring of the safety concern in clinical practice and encourage reporting, or provide information about means to minimise the potential risk); or
• A need for communication of other important information, in particular where the issue has been/is the subject of significant media coverage.
• In cases where a regulatory agency outside Saudi Arabia independently requests dissemination of a DHPC in their territory for a product also authorised in Saudi Arabia, the MAH should notify SFDA. The need for any subsequent action in Saudi Arabia should be considered and agreed on a case-by-case basis.

A DHPC should not be used to provide safety information which does not require urgent communication or is otherwise important to be communicated to Healthcare Professionals at individual level, such as changes to the SPC which do not impact on the conditions of appropriate use of the medicinal product.
1.5. Key Principles for Preparation of Texts for Direct Healthcare Professional Communications

When drafting a DHPC, the Template (see Annex 5.3.1) and the guidance provided there should be followed as appropriate, together with the principles described below:

- The message of the DHPC should be clear and concise with regard to the safety concern. It should not exceed two pages.
- The reason for dissemination of a DHPC at a particular point in time should be explained.
- Recommendations to Healthcare Professionals on how to minimise the risk should be provided if known.
- The safety concern should be placed in the context of the overall benefit of the treatment and not be presented as stand-alone information.
- The MAH should ensure that pharmacovigilance information to the general public (this includes Healthcare Professionals) is presented objectively and is not misleading.
- In general, the texts of DHPCs should be reviewed by, or if the timetable allows, tested among representatives of the target groups of Healthcare Professionals in order to assess clarity and understanding of the risk and expected adherence to the recommendations provided in the DHPC. Alternatively, standard phrases may be tested and subsequently used, as appropriate, particularly in urgent situations.
- In order to allow Healthcare Professionals to prepare responses to questions from Patients, the DHPC should also include the content of any information communicated directly to the general public. In case of suspension, withdrawal or revocation of a marketing authorisation, the DHPC should detail the type and procedure of recall of the medicinal product(s) from the market (e.g. pharmacy or patient level, date of recall).
- Public communication of the safety information issued to any target population by other Competent Authorities and other public bodies, ideally within and outside Saudi Arabia, should be taken into account.
- The DHPC should include a reminder of the need to report suspected adverse reactions in accordance with national spontaneous reporting systems.
- The estimated timeschedule for follow-up action, if any, by SFDA or the MAH should be provided.
- A list of contact points for further information, including website address(es), telephone numbers and a postal address to write to, should be provided at the end of the DHPC.
- A list of literature references should be annexed, when relevant.
- The DHPC may include a statement indicating that the DHPC has been agreed with SFDA.

1.6. The Processing of Direct Healthcare Professional Communications

1.6.1. The Roles and Responsibilities of MAHs and SFDA

The Competent Authorities are those who have issued a marketing authorisation for the medicinal product concerned.

Where the MAH proposes or is requested by SFDA to disseminate a DHPC, SFDA should be provided with:
- the proposed Communication Plan; including
- the proposed communication text of the DHPC; and
- the proposed texts of any related communication documents (see Chapter III.1, Section 6.2.(2)).
The timing of the submission should allow SFDA reasonable time (a minimum of two working days) to comment on the Communication Plan and the proposed communication texts prior to their finalisation. Exceptionally, less than two working days may be acceptable in the case of some urgent safety restrictions. The MAH should take into account comments from SFDA and discuss any outstanding issues when finalising these proposals. Ideally, the MAH should closely cooperate with the SFDA to finalise the text of the DHPC. The final Communication Plan and communication texts should be submitted to SFDA.

### 1.6.2. Phased Approach to Processing

The processing of a DHPC consists of four phases:

1. **Consideration phase: Initiation of the process**

   The process may be initiated by the MAH or the SFDA.

   When the MAH considers that a DHPC may be necessary, SFDA should be contacted and the documents required for the preparation of the DHPC submitted, as set out below. When SFDA considers that a DHPC may be necessary, it is recommended that the SFDA sends a request letter (in case of urgency the MAH may additionally be contacted by telephone and/or e-mail) requesting preparation of a draft DHPC and a Communication Plan. This request letter should provide the rationale for the request and the timetable for submission. When a request letter is received, the MAH should designate a contact point within the company for liaison with the SFDA.

   If the MAH considers that a DHPC is not appropriate or requires additional clarification, a written request may be submitted to the SFDA. In cases where agreement cannot be reached regarding dissemination of a DHPC by the MAH, a DHPC and/or a Public Statement may be issued by the SFDA.

   There may be situations in which more than one MAH is involved in the dissemination of a DHPC, e.g. where an interaction, a class-effect or generic medicinal products are concerned. In such situations, the objective is to provide consistent information to Healthcare Professionals and to avoid multiple DHPCs on the same safety concern from different MAHs which may lead to confusion. Where the number of MAHs involved is limited to two or three, they should work together to issue a single DHPC. For a larger number of MAHs or if a single joint DHPC is not agreed, the SFDA may opt to issue the DHPC.

2. **Pre-communication phase: Preparation of a DHPC**

   Once the intention to disseminate a DHPC is confirmed, the MAH should submit a draft Communication Plan including the following:

   - the objective of the DHPC and the draft DHPC and other communication texts (including amendments to the Product Information (SPC, Package Leaflet and Labelling), either mentioned in the DHPC text or, preferably, appended to the draft DHPC, if the final revised Product Information is available) as well as the key message to the public;
   - a proposed timetable covering the pre-communication, communication and post-communication phases with regard to all communication and other relevant documents including translations (see Chapter III.1, Section 6.3). This timetable should include:
     - timelines for comments on the Communication Plan and draft communication texts by SFDA;
     - timelines for agreement on final texts between the MAH and SFDA;
     - timelines for agreement on the date and time of release of the DHPC and information to the general public.
• any draft Communication Plans and communication texts under discussion with other Competent Authorities (outside Saudi Arabia for authorised products).
• a list of proposed recipients (target groups, e.g. general practitioners, specialists, coroners, pharmacists, nurses; hospitals/ambulatory care/other institutions), if appropriate;
• a description of the dissemination mechanism in Saudi Arabia where the DHPC is planned to be disseminated (e.g. by post);
• a plan for user testing of the communication text, if appropriate;
• a list of related communication documents, if appropriate, e.g. press release, questions & answers document, patient information sheet, and a description of their dissemination mechanisms in Saudi Arabia where the DHPC is planned to be disseminated;
• a description of the strategy for the post-communication phase, including the evaluation of the effectiveness of the DHPC, as outlined below in this Section, No 4.;
• an outline of proposed follow-up action and a draft Letter of Undertaking from the MAH on further investigations, if applicable; and
• a list of contact details of relevant partners.

The proposed time and date for distribution should be considered carefully, with dissemination of a DHPC at the beginning of a week considered ideal; however the release of urgent information should not be delayed for this reason.

When defining the target groups of recipients, it should be recognised that it is not only important to communicate with those Healthcare Professionals 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 who serve as information providers within healthcare systems and provide assistance and information to Patients, Healthcare Professionals, including hospital wards and poison centres, as well as the general public, in particular where media interest has arisen. The national professional associations of physicians, nurses and pharmacists should systematically receive DHPCs for further dissemination of the information to their members beyond the primary target groups of recipients.

DHPCs should contain an identification such as specific identifiers on the envelope (e.g. prominent red box warning) or use of a specific colour of notepaper. The use of such specific identifiers is encouraged to facilitate identification and focus Healthcare Professionals’ attention.

3. Communication phase: Dissemination of the DHPC

Implementation of the communication phase should adhere to the Communication Plan agreed between the MAH and the SFDA and should be accompanied by close monitoring of events by all partners. Any significant event or problem occurring during the communication phase should be communicated immediately between all relevant partners. If this reveals a need to change the Communication Plan or a need for further communication to Healthcare Professionals, this should be agreed between the MAH and the SFDA.

4. Post-communication phase: Follow-up of the DHPC

After dissemination of a DHPC, a closing review should be performed by the MAH, identifying any event or problem occurring during the communication phase requiring a change to the Communication Plan, any non-adherence to the Communication Plan as well as any difficulties experienced during any of the above phases. Such difficulties may relate e.g. to the list of recipients or the date and mechanism of dissemination. The SFDA should be informed of the outcome of this closing review and should also inform the MAH of difficulties they identified. If the SFDA is not satisfied, a written request should be made to the MAH to correct the situation. On the basis of this information, action should be taken to prevent or anticipate similar problems in the future. All partners should also perform internal reviews of their performance as part of integrated
quality management and take appropriate action for improvement as needed. In general, evaluation of the public health impact and the effectiveness of DHPCs should be performed in order to evaluate if the DHPCs have been received in a timely manner (check in a small sample of the target population) and if the recommendations and key messages have been understood and followed (e.g. by means of healthcare professional surveys or other study designs). This evaluation should be performed by the Marketing Authorisation Holder and is specifically relevant where DHPCs are part of risk minimisation activities in accordance with the applicable Risk Management Plan (see Chapter I.3).

1.6.3. Translations

For authorised products, the proposed communication texts will be submitted in English as working language.

Once the communication texts are agreed with the SFDA, the MAH should prepare translations of the DHPC in Arabic language.

The draft translations should be submitted to SFDA for a language review within a reasonable time (minimum of one working day). The MAH should take account of comments from SFDA and discuss any outstanding issues when finalising translations.

2. Collaboration with the World Health Organization

2.1. Introduction

SFDA shall collaborate with the World Health Organization (WHO) in matters of international pharmacovigilance and shall submit promptly to WHO appropriate and adequate information regarding the measures taken in Saudi Arabia which may have a bearing on public health protection worldwide.

In addition, it should be noted that the SFDA, may give a scientific opinion, in the context of cooperation with WHO, for the evaluation of certain medicinal products for human use intended exclusively for markets outside Saudi Arabia.

This Chapter describes the principles for providing WHO with pharmacovigilance information on measures taken for medicinal products in Saudi Arabia and other collaboration with WHO in the field of pharmacovigilance. The SFDA is a member of the WHO Program for International Drug Monitoring and should fulfill their membership obligations accordingly.

2.2. Provision of Individual Case Safety Reports

Cases of adverse reactions occurring in Saudi Arabia should be reported to the WHO Collaborating Centre by SFDA, in accordance with the agreements between the WHO Collaborating Centre and countries participating in the WHO Program for International Drug Monitoring. This applies to adverse reaction case reports for authorised medicinal products submitted to the SFDA either by Healthcare Professionals or by the MAHs.
2.3. **Review of Signals Raised by the WHO Collaborating Centre**

SFDA, should consider the summary document on signals provided by the WHO Collaborating Centre as feedback information from their case report database, Vigibase. This database may be consulted by all countries participating in the WHO Programme for International Drug Monitoring.

2.4. **Participation in the Annual Meetings of the WHO Program for International Drug Monitoring**

SFDA representative should attend regularly the Annual Meetings of the WHO Program for International Drug Monitoring, participating, as appropriate, in the exchange of information and data on topics of common concern and of interest to international pharmacovigilance.
PART 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 SFDA. It should be read in conjunction with the other pharmacovigilance guidelines contained in this document of the Rules Governing medicinal products in Saudi Arabia. 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 vaccine 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 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 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 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, 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 vaccinee 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 post-authorisation 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 pre-authorisation 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 pre-authorisation 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, 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, 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 Chapter I.3 of the Rules Governing medicinal products in Saudi Arabia. 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 post-authorisation 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 Saudi Arabia 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 Saudi Arabia 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 post-authorisation 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 Collaboration(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 re-exposure 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 under-estimate 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 pre-requisite 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.

The guidance on PASS in Chapter I.7 should be followed.

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 on 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 vaccinee 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 Summary of Product Characteristics (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.
ANNEXES
ANNEX (1)

1. Glossary

1.1. General

Abuse of a medicinal product, synonym: Drug abuse

Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects.

Adverse event (AE), synonym: Adverse experience

Any untoward medical occurrence in a patient or clinical-trial subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction, synonym: Adverse drug reaction (ADR), Suspected adverse (drug) reaction

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (see ICH-E2A see Annex 4).

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

See also under Adverse event, Serious adverse reaction, Unexpected adverse reaction, Listed adverse reaction, Reportable adverse reaction, Unlisted adverse reaction

Clinical trial

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the objective of ascertaining its (their) safety and/or efficacy; This includes clinical trials carried out in either one site or multiple sites.

An investigational medicinal product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Consumer

A person who is not a Healthcare Professional such as a Patient, lawyer, friend or relative/parents/children of a Patient.

Company Core Data Sheet (CCDS)

A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI)

All relevant safety information contained in the company core data sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the product, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Data lock point

The date designated as the cut-off date for data to be included in a Periodic Safety Update Report.

Drug abuse

See under Abuse

Saudi Birth Date (SBD)

The date of the first marketing authorisation for a medicinal product granted in Saudi Arabia to the MAH.

See also International Birth Date

Healthcare Professional

For the purposes of reporting suspected adverse reactions, Healthcare Professionals are defined as medically qualified persons, such as physicians, dentists, pharmacists, nurses and coroners.

Individual Case Safety Report (ICSR), synonym: Safety report

A document providing the most complete information related to an individual case at a certain point of time. An individual case is the information provided by a primary source to describe suspected adverse reaction(s) related to the administration of one or more medicinal products to an individual Patient at a particular point of time.

International Birth Date (IBD)

The date of the first marketing authorisation for a medicinal product granted to the MAH in any country in the world. For a medicinal product for which the International Birth Date is not known, the MAH can designate an International Birth Date to allow synchronisation of submission of Periodic Safety Update Reports.
Invented name

The name of a medicinal product as it appears in the Product Information, or the common or scientific name together with a trademark or the name of the MAH followed by the strength and the pharmaceutical form of the product.

The common name is the International Non-proprietary Name (INN) recommended by the World Health Organization, or if one does not exist, the usual common name.

Listed adverse reaction

An adverse reaction whose nature, severity, specificity and outcome are consistent with the information in the company core safety information.

Medicinal product

• Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
• Any substance or combination of substances 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.

Non-interventional trial

A study where the medicinal product(s) is (are) 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 the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data.

Periodic Safety Update Report (PSUR)

Periodic safety update reports mean the periodical reports containing the records referred to in Chapter I.6.

Post-authorisation study

Any study conducted within the conditions laid down in the Summary of Product Characteristics and other conditions laid down for the marketing of the product or under normal conditions of use. A post-authorisation study falls either within the definitions of a clinical trial or a non-interventional study and may also fall within the definition of a post-authorisation safety study.

See also under Clinical trial, Non-interventional trial and Post-authorisation safety study

Post-authorisation safety study (PASS)

A pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorised medicinal product.

See also under Clinical trial and Non-interventional trial
Risk-benefit balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks (any risk relating to the quality, safety or efficacy of the medicinal product as regards Patients’ health or public health).

See also under Risks related to use of a medicinal product

Risk management system

A risk management system shall comprise 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 interventions.

Risks related to use of a medicinal product

Any risk relating to the quality, safety or efficacy of the medicinal product as regards Patients’ health or public health and any risk of undesirable effects on the environment.

Serious adverse reaction

Serious adverse reaction means an adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.

Life threatening in this context 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 and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the Patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

See also under Adverse reaction

Solicited sources of Individual Case Safety Reports

Organised data collection schemes which include clinical trials, registries, named-patients use programmes, other patient support and disease management programmes, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

For the purpose of safety reporting, solicited reports should be classified as Individual Case Safety Reports from studies and therefore should have an appropriate causality assessment by a Healthcare Professional or the MAH.

See also under Clinical trial, Non-interventional trial and Post-authorisation safety study
**Spontaneous report, synonym: Spontaneous notification**

An unsolicited communication by a Healthcare Professional or Consumer to a company, regulatory authority or other organisation (e.g. WHO, a regional centre, a poison control centre) which fulfills the following three conditions:

- it describes one or more suspected adverse reactions in a patient
- the patient was given one or more medicinal products
- it does not derive from a study or any organised data collection scheme.

Healthcare Professionals or Consumers may be stimulated to report a suspected adverse reaction by several situations including:

- a Direct Healthcare Professional Communication
- Early Post-Marketing Phase Vigilance (EPPV), e.g. in Japan
- a report in the press
- direct questioning of Healthcare Professionals by company representatives.

In these circumstances, provided the report meets the three conditions above, it should be considered a spontaneous report.

**Unexpected adverse reaction**

An adverse reaction, the nature, severity or outcome of which is not consistent with the Summary of Product Characteristics (SPC). This includes class-related reactions which are mentioned in the SPC but which are not specifically described as occurring with this product.

**Unlisted adverse reaction**

An adverse reaction that is not specifically included as a suspected adverse effect in the Company Core Safety Information (CCSI). This includes an adverse reaction whose nature, severity, specificity or outcome is not consistent with the information in the CCSI. It also includes class-related reactions which are mentioned in the CCSI but which are not specifically described as occurring with this product.
1.2. Terms in Relation to Risk Management

Additional risk minimisation activity

A risk minimisation activity put in place to reduce the probability of an adverse reaction occurring or its severity should it occur which is not a routine risk minimisation activity – e.g. additional educational material or use of one of the other risk minimisation activities in Table I.3.A.

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks 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 (placebo or active substance, or unexposed 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.

Important identified risk, important potential risk or important missing information

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

Missing information

Information about the safety of a medicinal product which is not available at the time of submission of the Risk Management Plan and which represents a limitation of the safety data with respect to predicting the safety of the product in the marketplace.

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 of potential risks include:

- Non-clinical safety concerns that 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 the 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 which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.

See Adverse Event
Risk management system

A risk management system shall comprise 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 interventions.

Risk minimisation

This is a set of activities used to reduce the probability of an adverse reaction occurring or its severity should it occur.

Routine pharmacovigilance

Pharmacovigilance activities that should be conducted for all medicinal products.

Routine risk minimisation activities

The warnings and information contained within the Summary of Product Characteristics and Patient Leaflet, and the careful use of labelling and packaging, which aim to reduce the probability of an adverse reaction occurring or its severity should it occur.

Safety concern

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

Target Population

The Patients who might be treated by the medicinal product according to the indication(s) and contraindication(s) in the Summary of Product Characteristics.
1.3. Terms in Relation to Electronic Exchange of Pharmacovigilance Information Applicant

**Applicant**

A pharmaceutical company applying for a marketing authorisation in Saudi Arabia.

**Electronic data interchange (EDI)**

Electronic transfer, from computer to computer, of commercial and administrative data using an agreed standard to structure an EDI message. EDI is based on the use of structured and coded messages, the main characteristic of which is their ability to be processed by computers and transmitted automatically and without ambiguity. This makes EDI specific in comparison with other data exchange such as electronic mail.

**SaudiVigilance database management system**

The pharmacovigilance database defined in the National Pharmacovigilance Guidelines.

**SaudiVigilance gateway**

The data-processing network as defined in the guidelines that provides a single point of contact between MAHs, Applicants, sponsors and SFDA in Saudi Arabia. By doing so, the SaudiVigilance Gateway is considered a hub and all connections to the EDI Partners are known as spokes. Safety, Acknowledgement and medicinal product Report Messages are routed through the hub to the desired spoke.

**Extensible markup language (XML)**

A subset of SGML that is completely compatible with SGML.

**Gateway**

A data exchange service, which consists of all core standards and functionality required for supporting the ICH standards (e.g. Simple Mail Transfer Protocol (SMTP)/Secure Multipurpose Internet Mail (SMIME)).

**Individual case**

The information provided by a primary source to describe suspected adverse reaction(s)/suspected unexpected serious adverse reactions related to the administration of one or more medicinal products/investigational medicinal products to an individual patient at a particular point of time.

**Investigational medicinal product (IMP)**

A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.
Medicinal product file

The electronic file transmitted in one Message Transaction between one Sender and one Receiver containing one Medicinal product Report Message.

Medicinal product report (MPR)

An electronic report with a defined set of data elements to populate and update the Saudi Vigilance medicinal product Dictionary. A medicinal product Report may contain information on an authorised medicinal product/investigational medicinal product.

Sponsor

An individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial.
ANNEX (2)

2. Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR</td>
<td>Adverse drug reaction</td>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>ATC</td>
<td>Anatomical-Therapeutic-Chemical Classification</td>
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<tr>
<td>CCDS</td>
<td>Company Core Data Sheet</td>
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<tr>
<td>CCSI</td>
<td>Company Core Safety Information</td>
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<tr>
<td>CV</td>
<td>Curriculum (Curricula) Vitae</td>
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<td>DHPC(s)</td>
<td>Direct Healthcare Professional Communication(s)</td>
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<td>DUS</td>
<td>Drug utilisation studies</td>
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<tr>
<td>EDI</td>
<td>Electronic data interchange</td>
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<tr>
<td>EMEA</td>
<td>European Medicines Agency; “the Agency”</td>
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<tr>
<td>FDA</td>
<td>US Food and Drug Administration</td>
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<tr>
<td>IBD</td>
<td>International Birth Date</td>
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<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<td>Individual Case Safety Report(s)</td>
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<td>IMP</td>
<td>Investigational Medicinal Product</td>
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<td>IT</td>
<td>Information Technology</td>
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<td>ISPE</td>
<td>International Society for Pharmacoepidemiology</td>
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<td>LLTs</td>
<td>Lowest Level Terms (of MedDRA)</td>
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<td>Medical Dictionary for Regulatory Activities</td>
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<td>MPR</td>
<td>Medicinal Product Report</td>
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<td>NUI</td>
<td>Non-Urgent Information</td>
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<td>NPC</td>
<td>National Pharmacovigilance Center</td>
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<td>Public Assessment Report</td>
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<td>PASS</td>
<td>Post-authorisation safety study</td>
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<tr>
<td>PL</td>
<td>Package Leaflet</td>
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<td>PSUR(s)</td>
<td>Periodic Update Safety Report(s)</td>
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<td>QPPV</td>
<td>Qualified Person Responsible for Pharmacovigilance</td>
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<td>Saudi Arabia Birth Date</td>
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<td>SFDA</td>
<td>Saudi Food and Drug Authority</td>
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<td>SOCs</td>
<td>System Organ Classes (of MedDRA)</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<td>SUSAR(s)</td>
<td>Suspected unexpected serious adverse reaction(s)</td>
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<td>USR</td>
<td>Urgent safety restriction</td>
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<td>World Health Organization</td>
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ANNEX (3)
3. Other Guidelines and Relevant Terminology

3.1. Other Pharmacovigilance Guidelines

3.1.1. Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRs) in Pharmacovigilance During the Pre- and Post-Authorisation Phase in the European Economic Area (EEA)

Adopted at Community level in September 2004.


3.1.2. Guideline on the Exposure to Medicinal Products During Pregnancy: Need for Post-Authorisation Data

This Guideline (EMEA/CHMP/313666/2005) is available on the EMEA website http://www.emea.europa.eu.

3.1.3. Guideline on the Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population

This Guideline (EMEA/CHMP/PhVWP/235910/2005) is available on the EMEA website http://www.emea.europa.eu.

3.2. Relevant Terminology

3.2.1. Medical Terms

See Annex 4.5 for Dictionary for Regulatory Activities (MedDRA).

3.2.2. Standard Terms on Pharmaceutical Dosage Forms, Routes of Administration and Containers

These Standard Terms are published by the Council of Europe and are available on the website of the European Pharmacopoeia http://www.pheur.org.

3.2.3. Controlled Vocabulary for Routes of Administration

See Annex 4.7.1

3.2.4. Controlled Vocabulary for Units and Measurements

See Annex 4.7.2
ANNEX (4)

4. ICH Guidelines

4.1. ICH-E2B(M) - Maintenance of the Clinical Safety Data Management Including: Data Elements for Transmission of Individual Case Safety Reports

This Guideline is published under document reference number CPMP/ICH/287/95 modification corr. on the EMEA website www.emea.europa.eu.

4.1.1. ICH- E2B Q&As (R5): Questions and Answers Data Elements for Transmission of Individual Case Safety Reports

This Guideline is published under document reference number CPMP/ICH/3943/03 on the EMEA website www.emea.europa.eu.

4.2. ICH-E2C(R1): Clinical Safety Data Management - Periodic Safety Update Reports for Marketed Drugs including Addendum to ICH-E2C


4.3. ICH-E2D: Post-Approval Safety Data Management - Definitions and Standards for Expedited Reporting

This Guideline is published under document reference number CPMP/ICH/3945/03 on the EMEA website www.emea.europa.eu.

4.4. ICH-E2E: Pharmacovigilance Planning

This Guideline is published under document reference number CPMP/ICH/5716/03 on the EMEA website www.emea.europa.eu.

4.5. ICH-M1: Medical Terminology - Medical Dictionary for Regulatory Activities (MedDRA)

Reference to the recommendations can be found on the EMEA website www.emea.europa.eu.

Reference to the recommendations can be found on the EMEA website www.emea.europa.eu.

4.7. ICH-M5: Data Elements and Standards for Drug Dictionaries

4.7.1. Routes of Administration Controlled Vocabulary

This Guideline is published under document reference number HMP/ICH/175860/05 on the EMEA website www.emea.europa.eu.

4.7.2. Units and Measurements Controlled Vocabulary

This Guideline is published under document reference number CHMP/ICH/175818/05 on the EMEA website www.emea.europa.eu.

4.8. ICH-E2A: Clinical Safety Data Management-Definitions and Standards For Expedited Reporting

This Guideline is published on FDA website www.fda.gov/cder/guidance/ich2a
ANNEX (5)

5. Templates

5.1.1. Template for SFDA Risk Management Plan (SFDA – RMP)
Details of this Template will be available on SFDA website www.sfda.gov.sa after completion.
5.2.1. Template for Cover Page for PSUR Submission

<Serial number> PERIODIC SAFETY UPDATE REPORT for
ACTIVE SUBSTANCE(S): <INN>
ATC CODE(S): <Code(s)>

MEDICINAL PRODUCTS COVERED:

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INTERNATIONAL BIRTH DATE (IBD): <Date>

PERIOD COVERED BY THIS REPORT:
from <Date> to <Date (i.e. data lock point)>
DATE OF THIS REPORT: <Date>

OTHER INFORMATION:
<Other identifying or clarifying information if necessary>
DATA LOCK POINT OF NEXT PSUR: <Date>

MAH'S NAME AND ADDRESS:
>Name>
<Address>

NAME AND CONTACT DETAILS OF THE QPPV:
>Name>
<Address>
<Telephone number>
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SIGNATURE: <Signature>

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5.2.2. Template for PSUR section "Worldwide Marketing Authorisation Status"

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<td>AQ - 3/92</td>
<td>6/92</td>
<td>Bacgone</td>
<td>Elderly (&gt; 65) excluded</td>
</tr>
<tr>
<td></td>
<td>A - 4/94</td>
<td>7/94</td>
<td>Bacgone-C (skin inf)</td>
<td>(PK)</td>
</tr>
<tr>
<td>Japan</td>
<td>LA - 12/92</td>
<td>-</td>
<td>-</td>
<td>To be refilled</td>
</tr>
<tr>
<td>France</td>
<td>V - 9/92</td>
<td>-</td>
<td>-</td>
<td>Unrelated to safety</td>
</tr>
<tr>
<td>Nigeria</td>
<td>A - 5/93</td>
<td>7/93</td>
<td>Bactoff</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>A - 9/93</td>
<td>1/94</td>
<td>Bactoff</td>
<td>New indication</td>
</tr>
</tbody>
</table>

**Abbreviations:** A = authorised; AQ = authorised with qualifications; LA = lack of approval; V = voluntary marketing application withdrawal by company; AR = authorisation renewal.
5.2.3. Template for PSUR section "Line-listings of Individual Case Histories"

<table>
<thead>
<tr>
<th>MAH NO</th>
<th>COUNTRY</th>
<th>SOURCE</th>
<th>AGE/SEX</th>
<th>DAILY DOSE mg/day</th>
<th>DATE OF ONSET OF REACTION or time to onset</th>
<th>DATES OF TREATMENT or treatment duration</th>
<th>REACTION DESCRIPTION</th>
<th>OUTCOME</th>
<th>COMMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>
### 5.2.4. Template for PSUR section "Summary Tabulations"

This table is only one example of different possible data presentations which are at the discretion of the MAH (e.g.: serious and non-serious in the same table or as separate tables, etc.).

Number of Reports by Term (Signs, Symptoms and Diagnoses) from Spontaneous (Medically Confirmed), Clinical Study and Literature Cases:

All Serious Reactions

An * indicates an unlisted reaction

<table>
<thead>
<tr>
<th>Body system/Adverse reaction term</th>
<th>Spontaneous/Regulatory bodies</th>
<th>Clinical studies</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>hallucinations*</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>etc.</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>etc.</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Sub-total</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>CV</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>etc.</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>etc.</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Sub-total</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td>Etc.</td>
<td>-----------------------------</td>
<td>-----------------</td>
<td>------------</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>-----------------------------</strong></td>
<td><strong>-----------------</strong></td>
<td><strong>------------</strong></td>
</tr>
</tbody>
</table>

In a footnote (or elsewhere), the number of patient-cases that represent the tabulated terms should be given (e.g.: x-spontaneous/regulatory, y-clinical study, and z-literature cases)
5.3.1. Template for Direct Healthcare Professional Communications (DHPCs)

<Date>

<Document reference number>

Direct Healthcare Professional Communication on the association of <INN and Invented Name(s)> with <safety concern>

**Summary**

<A brief description of the safety concern, recommendations for risk minimisation (e.g. contraindications, warnings, precautions of use) and, if applicable, switch to alternative treatment, preferably in bullet points>

<Recall information, if applicable (e.g. pharmacy or patient level, date of recall)>

<A statement indicating that the information has been endorsed by SFDA and the MAH, if applicable>

*Style guide:* The Summary section should be in larger font size than the other sections of the DHPC.

**Further information on the safety concern**

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, e.g. the pharmacodynamic mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors), also indicating the reason for disseminating the DHPC at this point in time>

<Placing of the risk in the context of the benefit>

<Revised Product Information text or, preferably, reference to revised Product Information in Annex>

<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>

<A statement indicating the context in which the assessment has been conducted>

<A schedule for follow-up action(s) by the MAH/SFDA, if applicable>

**Further information on recommendations to healthcare professionals**

<If needed, details on the recommendations for risk minimisation>

<If needed, additional detailed instructions on how to use the new safety or therapeutic effectiveness information>

**Call for reporting**

<A reminder of the need to report adverse reactions in accordance with the SaudiVigilance spontaneous reporting system>

<Details (name, postal address, fax number, website address) on how to access the SaudiVigilance spontaneous reporting system/Details on how to report to the MAH>

**Communication information**

<Date and key messages of communication to the public>

<Content and dissemination mechanism of information to the general public or Patients, if applicable>

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>
Annexes:
<Text of the revised Product Information (with changes made visible), if applicable>
<Detailed scientific information, if necessary>
<List of literature references, if applicable>
6. Classification of Batch Recalls for Quality Defects

6.1. Class 1:
Defects are potentially life-threatening or could cause a serious risk to health.
Examples:

6.1.1: Wrong product (label and contents are different products)
6.1.2: Correct product but wrong strength, with serious medical consequences
6.1.3: Microbial contamination of sterile injectable or ophthalmic product
6.1.4: Chemical contamination with serious medical consequences
6.1.5: Mix-up of some products (rogues) with more than one container involved
6.1.6: Wrong active ingredient in a multi-component product, with serious medical consequences.

6.2. Class 2:
Defects could cause illness or mistreatment, but are not Class 1.
Examples:

6.2.1: Mislabeling, e.g. wrong or missing text or figures
6.2.2: Missing or incorrect information (leaflets or inserts)
6.2.3: Microbial contamination of non-injectable, non-ophtalmic sterile product with medical consequences
6.2.4: Chemical/physical contamination (significant impurities, cross-contamination, particulates)
6.2.5: Mix up of products in containers (rogues)
6.2.6: Non-compliance with specification (e.g. assay, stability, fill/weight)
6.2.7: Insecure closure with serious medical consequences (e.g. cytotoxics, child- resistant containers, potent products).

6.3. Class 3:
Defects may not pose a significant hazard to health, but withdrawal may have been initiated for other reasons.
Examples:

6.3.1: Faulty packaging, e.g. wrong or missing batch number or expiry date
6.3.2: Faulty closure
6.3.3: Contamination, e.g. microbial spoilage, dirt or detritus, particulate matter
References


