

Guideline on Pharmacovigilance for Veterinary Products

Version 1.0

Date of publication	16 September 2019
Date of implementation	Optional: 20 January 2020
	Mandatory: 1 July 2020

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Saudi Food and Drug Authority

Vision and Mission

Vision

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

Mission

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

Document Control

Version	Author	Date	Comments
Draft	Executive Directorate of Pharmacovigilance	16 September 2019	Draft
1.0	Executive Directorate of Pharmacovigilance	20 January 2020	Final version

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PART I: Guidelines for Marketing Authorisation Holders

1. INTRODUCTION:

This guideline issued to setup the veterinary product's safety control and report procedures as one of the controlling procedures. Those procedures have been referred in the article 5 of the SFDA regulation that issue by Royale Decree (6/٢) on 25/1/1428 H”

“Article No.3 of (the GCC veterinary products directive and its executive regulation issued by the Royale Decree (17/٢) on 24/2/1435H, state clearly the responsibility of observing veterinary products post-marketing in order to receive defect reports from various stakeholders (see Annex 2. References).

The requirements explained in this guideline is based on mainly the European Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use (Volume 9B) (see Annex 2. References).

2. GENERAL PRINCIPLES

2.1. Legal Basis of the Marketing Authorisation Holder’s Obligations for Pharmacovigilance

The article No.20 of the GCC veterinary products directive marketing authorization holders are obligated to report any side effects or any quality defects along with the marketing authorization status at the country of origin or elsewhere. This obligation to report any serious adverse event should take place within 15 days of its occurrence according to article No.18 of the GCC veterinary products executive regulation and 72 hours for of serious and unexpected adverse events according to article No.5 (9) of the GCC veterinary products executive regulation (see Annex 2. References).

2.2. Roles and Responsibilities of the Marketing Authorisation Holder and The Qualified Person Responsible for Pharmacovigilance

The MAH should ensure that it has an appropriate system of pharmacovigilance in place in order to assume responsibility and liability for its veterinary products on the market and to ensure that appropriate action may be taken, when necessary. The MAH should therefore ensure that new information relevant to the benefit-risk balance of a veterinary products is reported to SFDA fully and promptly in accordance with the legislation, in accordance with Article 5 (8, 9, 10, and 11) of the GCC veterinary products executive regulation (see Annex 2. References).

When applying for a Marketing Authorisation (MA), the Applicant, in preparation for the role and responsibilities as MAH, should submit a Detailed Description of the Pharmacovigilance System (DDPS) and, where appropriate, of the risk management system, and submit proof that the services of a Qualified Person Responsible for Pharmacovigilance (QPPV) are in place accordance with Article 5 (8) of the GCC veterinary products executive regulation.

The role of the QPPV is very important, and this Chapter therefore describes the role and responsibilities of the QPPV and provides guidance for the MAH on how to adequately support the QPPV.

It is preferable that one person is ultimately responsible for all aspects of the pharmacovigilance system of a company, and therefore each company (i.e. Applicant/MAH or group of MAHs using a common pharmacovigilance system) is strongly recommended to appoint one QPPV responsible for overall pharmacovigilance for all veterinary products for which the company holds MAs within Saudi Arabia a (see also Part I Chapter 3. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections).

The QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfil the responsibilities and tasks of the post. The QPPV should be a Saudi national veterinarian. If the QPPV is not a veterinarian then QPPV must be a Saudi with bachelor degree in pharmaceutical sciences with documented experience in veterinary medicines and direct access with veterinarian.

The name and contact details, including out-of-office hours' details, of the QPPV and back-up procedures to ensure business continuity and continued fulfilment of pharmacovigilance obligations should be notified to SFDA.

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

The QPPV is responsible for

- the establishment and maintenance of a pharmacovigilance system which ensures that information about all adverse events which are reported to any personnel of the MAH, is collected and collated in order to be accessible at least at one point;
- Detailed guidance for the preparation of these reports are included in Part I:
 - Chapter 5. Adverse Event Reporting,
 - Chapter 6. Requirements for Periodic Safety Update Reports, and
 - Chapter 7. Company-Sponsored Post-Authorisation Safety Studies;
- The conduct of continuous overall pharmacovigilance evaluation during the post-authorisation period (see Part I Chapter 8. Overall Pharmacovigilance Evaluation and Safety-Related Regulatory Action);

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 above system components and processes, either directly or through supervision.

The oversight referred to above should cover the functioning of the MAHs 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 timelines for expedited reporting and submission of PSURs),
- Audit reports
- Training of personnel in relation to pharmacovigilance.

It is recognised that this role of the QPPV may impose extensive tasks on the QPPV, depending on the size and nature of the pharmacovigilance system and the number and type of Veterinary Products for which the MAH holds MAs. The QPPV may therefore delegate specific tasks, under supervision, to appropriately qualified and trained individuals, e.g. acting as experts on the safety aspects of certain Veterinary Products, provided that the QPPV maintains system oversight and overview of the safety profiles of all Veterinary Products.

In case of absence, the QPPV should ensure that all responsibilities are undertaken by an adequately qualified person. This person and the QPPV should also reside in Saudi Arabia.

The QPPV should also act as the MAHs contact point for pharmacovigilance inspections or should be made aware by the MAH of any inspection and be contactable and ideally be available during inspection.

2.2.2. Responsibilities of the Marketing Authorisation Holder in relation to the Qualified Person responsible for Pharmacovigilance:

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 fulfilment 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 benefit-risk 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 Veterinary Products, 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 MAHs pharmacovigilance system in order to promote, maintain and improve compliance; and
- to provide input into the preparation of regulatory action in response to emerging safety concerns (e.g. variations, urgent safety restrictions, and, as appropriate, communication to the general public).

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).

2.3. Contractual Arrangements

A MAH may transfer certain pharmacovigilance tasks and functions to organisation, but the ultimate responsibility for the fulfilment 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 clearly documented contractual arrangements for meeting pharmacovigilance obligations are in place between MAHs and organisations involved in the fulfilment of pharmacovigilance obligations and to provide SFDA with information on such arrangements in line with the requirements set out in Part I Chapter 3. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections. The contracted organisation should implement quality assurance and quality control and accept to be audited by or behalf of the MAH. In cases of contractual arrangements between MAHs in relation to co-marketing of separately authorised veterinary products, which are identical in all aspects apart from their invented names, these arrangements should include measures to avoid the duplicate submission of adverse events to SFDA.

3. REQUIREMENTS FOR PHARMACOVIGILANCE SYSTEMS, MONITORING OF COMPLIANCE AND PHARMACOVIGILANCE INSPECTIONS

3.1. Introduction

The rapid and effective identification and assessment of safety issues concerning veterinary products is dependent on early access to complete information. This is fundamental to SFDA and MAHs ability to protect public or animal health in taking appropriate action swiftly. MAHs, SFDA have an obligation to implement legislation concerning veterinary products. Non-compliance with pharmacovigilance regulatory obligations could have a potentially serious health impact.

This Chapter sets out the framework 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 Marketing Authorisation Application (MAA) giving a Detailed Description of the Pharmacovigilance System (DDPS) of the MAH and proof that the MAH has the services of a QPPV and the necessary means for the notification of adverse events. This guidance is applicable for any veterinary products, whatever the MA procedure used.

3.2.Detailed description of the pharmacovigilance system

3.2.1. Location of the detailed description in the application for a marketing authorisation and update of the detailed description:

The DDPS, 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 event.

The DDPS 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 this should be indicated in a product specific addendum.

The DDPS should be supported by documentation maintained by the company.

Updates to the information provided in the DDPS should be made in accordance with current legislation.

3.2.2. 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 event.

3.2.3. Elements of the detailed description of the pharmacovigilance system that should be described in the application for a marketing authorisation:

All MAHs are required to have an appropriate system of pharmacovigilance in place. The DDPS 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:

a) QPPV

- The name of the QPPV located in Saudi Arabia a. The business address and contact details should be provided in the MAA 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 (CV) 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.

b) Organisation

- Identification and location of the company units or other organisations where the principal local and global pharmacovigilance activities are undertaken (in particular those sites Where the main databases are located, where adverse events are collated and reported and where PSURs are prepared and processed.

- Identification of the point(s) in Saudi Arabia at which pharmacovigilance data are accessible (to include access to adverse events, PSURs and the global pharmacovigilance data).
- High level organisation chart(s) providing an overview of the global and Saudi Arabia a 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 Saudi Arabia a QPPV within the organisation. Individual names of people should not be included here. Licensing partnerships are usually product specific and should be indicated in a product specific addendum, in the MAA 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 SFDA. These should be limited to the major processes.

c) Procedures in place, which are documented in writing

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 DDPS 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, veterinary review and reporting of adverse events:
 - 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 veterinarians and other health care professionals, animal owners, sales and marketing personnel.
 - 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
 - PSURs: The preparation, processing, quality control, review including veterinary review and reporting.
- Global pharmacovigilance activities applying to all products: Continuous safety profile of authorised veterinary products (product-specific risk management and pharmacovigilance planning are not addressed in this Chapter):
 - Signal detection and review,
 - Benefit-risk assessment,
 - Reporting and communication notifying health care professionals of changes to the risk-benefit balance of products, etc.
- Interaction between safety issues and product defects
- Responses to requests.
- Handling of urgent safety restrictions and safety variations
- Meeting commitments to competent authorities in relation to a marketing authorisations
- Management and use of databases or other recording systems
- Internal audit of the pharmacovigilance system
- Training
- Archiving

The DDPS should indicate the processes for which written procedures are available. A list and copies of the global and Saudi Arabia a procedure should be available within two working days after receipt by the MAH of SFDA's request.

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 as referred to in Part II: Guidelines for Marketing Authorisation Holders on Electronic Exchange of Pharmacovigilance Information.

e) Contractual arrangements with other 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.

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 within Saudi Arabia 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 MAA. Likewise, if subcontracting is product specific this should be indicated in a product specific addendum.

f) Training

Staff should be appropriately trained for performing pharmacovigilance related activities, taking into account their role within the company. This includes not only staff within the pharmacovigilance units but also staff who may receive or process safety reports, such as sales personnel, or field trial/clinical research staff. Provide a brief description of the training system and indicate where the training records, CVs and job descriptions are filed.

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 above under subheading “Organisation”.

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 where appropriate auditing of sub-contractors, should be provided.

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.

3.3. Monitoring of compliance

Guidelines, education programs, responding to enquiries and systems for electronic reporting have been developed to facilitate the MAHs to meet their obligations concerning pharmacovigilance. SFDA should monitor MAHs for compliance with pharmacovigilance regulatory obligations. Furthermore, SFDA shall exchange information in cases of non-compliance and will take appropriate regulatory action as required.

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 to SFDA. 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 DDPS, procedures, safety reports and through pharmacovigilance inspections.

3.3.1. Qualified Person for Pharmacovigilance:

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

3.3.2. Availability of pharmacovigilance data:

SFDA shall monitor (e.g. by assessment of the DDPS and when inspections are carried out) that pharmacovigilance data are collated and accessible by the MAH.

3.3.3. Change in the evaluation of the benefit-risk balance of a product:

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

3.3.4. Expedited adverse event reporting:

Requirements for expedited reporting of adverse events are given in Chapter 5. Adverse Event Reporting. Non-compliance with expedited reporting may include complete failure to report, delayed reporting (i.e. submission beyond 15 calendar 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 for monitoring of compliance with expedited reporting of adverse events could be:

- Monitoring adverse event 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 MAHs being scrutinised.
- Monitoring that all adverse events that are kept electronically comply with the requirements for electronic reporting set out in Part II: Guidelines for Marketing Authorisation Holders on Electronic Exchange of Pharmacovigilance Information.
- Checking 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 animal reports and human reactions have been submitted within 15 calendar 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 have been sent to SFDA electronic systems in place, and to confirm that procedures are in place to follow up reports.

3.3.5. Periodic Safety Update Reports:

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 other product information 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, non-restart of the cycle of submission when necessary.
- Incorrect format of the document: report not in accordance with Chapter 6. Requirements for Periodic Safety Update Reports.
- Omission of information required by Chapter 6. Requirements for Periodic Safety Update Reports, particularly in the following sections of the report: Update of regulatory competent authority or MAH actions taken for safety reasons, changes to the SPCs, animal exposure (including sales volume and numbers treated), PSUR line listing.
- Poor quality reports: poor documentation of adverse events or insufficient information provided to perform a thorough assessment in the section covering the narrative review of the individual case histories on basis of the line listing of individual reports, new safety signals not or poorly assessed in the section for overall safety information, misuse not highlighted, absence of standardised veterinary terminology.
- SPC: where unauthorized changes have been made to the SPC since the submission of the last PSUR. 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).

3.3.6. Requests for information from the 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 or animal 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.

3.3.7. 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 or animal 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.

3.3.8. Post-Authorisation Safety Studies:

Because of the objectives of post-authorisation 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 competent authorities of interim and final study reports from such studies has an important role in protecting public or animal health. Where appropriate, SFDA will scrutinise protocols prior to the initiation of post-authorisation safety studies. SFDA should check that relevant adverse event reports are expedited from those studies and will monitor the submission of interim and final study reports. Guidance on post-authorisation safety studies is available in Chapter 7. Company-Sponsored Post-Authorisation Safety Studies.

3.4. Pharmacovigilance inspections

To ensure that MAHs comply with their pharmacovigilance regulatory obligations and to facilitate compliance, SFDA will conduct pharmacovigilance inspections. There should be collaboration between SFDA to minimise duplication and maximise coverage. 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.

3.4.1. Conduct of inspections

In general, companies have a pharmacovigilance center in Saudi Arabia covering multiple veterinary products that are on the market shall be Inspected in accordance with this guidance.

3.4.2. Routine inspection

It is anticipated that SFDA pharmacovigilance inspection programmes will fulfil the need for routine inspections. They may be carried out on a repeated basis. The focus of these inspections is to determine that the MAH has personnel, systems and facilities in place to meet their regulatory obligations. These inspections may be requested with one or more specific veterinary 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. 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. These inspections will be prioritised based on the potential risk to public or animal health, the nature of the products, extent of use, number of products that the MAH has on Saudi Arabia a market and risk factors such as those identified under section 3.4.3 (Targeted inspections). This programmes will be separate from any targeted inspection, but if a targeted inspection takes place it may replace the need for one under this programmes dependent on its scope.

3.4.3. Targeted inspections:

Targeted inspections may be conducted as and when the trigger.

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 market in Saudi Arabia
- 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 etc)
- 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.
- Product withdrawal with little or no advance notice to 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.

3.4.4. 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.

3.4.5. 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 section 3.4.3.

3.4.6. Inspections of contractors, 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.

3.4.7. Procedures for Pharmacovigilance inspection

Procedures for pharmacovigilance inspection will be prepared in association with Pharmacovigilance inspectors and will be updated as needed.

3.4.8. Unannounced inspection

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.

3.4.9. 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 MAH.

3.4.10. 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.

3.5. Regulatory action

SFDA are obliged to implement pharmaceutical legislation and to ensure MAH compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance regulatory obligations is detected, the necessary action will be taken. The action taken will depend on the potential negative public or animal health impact of non-compliance but any instance of non-compliance may be referred for enforcement action.

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 reinspected to ensure compliance is achieved.
- Warning: SFDA may issue a formal warning reminding MAHs of their pharmacovigilance regulatory obligations.
- Urgent Safety Restriction
- Variation of the MA
- Suspension of the MA
- Revocation of the MA

4. REQUIREMENTS FOR RISK MANAGEMENT SYSTEMS

Risk management is defined as the process, distinct from risk assessment, of weighing policy alternatives, considering risk assessment and other factors relevant to ensure quality, safety (including environmental safety) and efficacy of the veterinary products.

Saudi FDA requires Applicants/MAHs to provide a description of risk management systems, when appropriate.

The risk management system is defined as a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those activities and interventions.

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 limited representation of target animals (number of animals, age, breeds etc.) used in the pre-clinical and clinical development of the product. Risks of many potentially affected subpopulations remain to be identified during the clinical use of the product.

Veterinary Products are authorized on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk is judged positive for the target population, the user, the consumer of food from food producing animals as well as the environment. However, not all actual or potential risks are identified when an initial marketing authorisation is granted.

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.

5. ADVERSE EVENT REPORTING

5.1. Introduction

The obligations of the MAH for recording and reporting adverse events associated with a veterinary product for which MAs are held are defined in the GCC veterinary products directive and its executive regulation. For adverse events, which are required to be reported within 15 calendar days ('expedited' reports), further explanation is provided in this Chapter. Reporting following suspension or withdrawal of the Marketing Authorisation for safety or commercial reasons is described in Part I Chapter 5. Reporting Following Suspension or Withdrawal of the Marketing Authorisation for Safety or Commercial Reasons.

For authorised veterinary products, independent of the authorisation procedure, adverse events received from veterinarians and other health-care professionals and other sources should be reported, regardless of whether or not the veterinary products were used in accordance with the authorised SPC and/or any other conditions laid down for marketing of the product in accordance with applicable legal requirements. Adverse events identified from the worldwide-published peer reviewed scientific literature should also be reported.

Electronic reporting of adverse events for MAH is mandatory, save in exceptional circumstances see Part II: Guidelines for Marketing Authorisation Holders on electronic

reporting of “expedited” as well as “non-expedited reports”. The definitions of ‘adverse reaction’, ‘serious adverse reaction’, ‘human adverse reaction’ and ‘unexpected adverse reaction’ are provided in the Glossary (see Annex 1. Glossary).

The definitions of ‘adverse event’, ‘serious adverse event’ and ‘unexpected adverse event’ are provided in the Glossary (see Annex 1. Glossary) and are based on the agreed terminology within the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (see Annex 2. References).

The MAH is expected to validate all adverse events reported by veterinarians and other health-care professionals and the general public to ensure, prior to reporting to SFDA, that the minimum information required is included in the report (see Section 5.5 Required information for adverse event reports). Reports should be followed-up to obtain additional information relevant to the case as necessary, and relevant follow-up information should be reported to SFDA. All available information relevant to the evaluation of the adverse reaction should be provided.

5.2. Requirements for expedited reporting

For all veterinary products, independent of the authorisation procedure, the MAH should report, on an expedited basis:

- all serious adverse events occurring in Saudi Arabia to SFDA.
- all serious and unexpected adverse events in animals, human adverse reactions and suspected transmission of infectious agents occurring in Saudi Arabia to SFDA database.

The definition of an ‘expedited report’ is provided in the Glossary (see Annex 1. Glossary).

In veterinary medicine the existence of a large diversity of animal species and husbandry conditions require a modified approach to the classification of a serious adverse event. For example, in intensive food animal production with species such as poultry, fish or bees, a certain level of mortality rate is considered as ‘normal’ or ‘expected’. These species are usually treated as a group/flock and only an increase of mortality rate, or severe signs, or animal production losses exceeding the rates normally expected should be considered as a serious adverse event. However, for food producing animals treated on an individual basis, an

individual death or severe symptoms should be regarded as a serious adverse event. Similarly, for companion animal species, like dogs and cats, a single death or severe symptoms constitutes a serious adverse event.

5.2.1. Reporting of serious adverse events including human adverse reactions:

The MAH should record and report all serious adverse events in animals and all human reactions occurring within Saudi Arabia which are brought to his attention, or of which he can reasonably be expected to have knowledge. These reports should be reported promptly, and in no case later than 15 calendar days from receipt, to SFDA. Receipt in this context means becoming aware of an adverse event. It should be noted that serious adverse events together with all other pharmacovigilance issues should be reported in the PSUR (see Chapter 6. Requirements for Periodic Safety Update Reports).

5.2.2. Reporting of serious and unexpected adverse events, including human adverse reactions, and transmission of infectious agents:

The MAH should report all serious and unexpected adverse events in animals (both criteria must apply), all human adverse reactions and any suspected transmission of an infectious agent relating to the use of veterinary products. These should be reported promptly, and no later than 3 calendar days following receipt to the SFDA database. In this context the relevant date of receipt of the information for Saudi regulatory purposes is considered to be the date of receipt of the information by the MAH and initial reporting may be limited to the minimum information constituting an adverse event report (See Section 5.5 Required information for adverse event reports).

5.2.3. Reporting of lack of expected efficacy:

Lack of expected efficacy is defined as the apparent inability of an authorised veterinary products to have the expected efficacy in an animal, according to the claims of the SPC and following use of the product in accordance with the SPC.

It is important in the first instance to clearly identify if the lack of expected efficacy is due to a possible batch quality problem.

Reports of suspected lack of efficacy should be recorded by the person responsible for pharmacovigilance and reported to SFDA in the same way as for all adverse events.

5.2.4. Reporting of adverse events following off-label use:

Off-label use is defined as the use of a veterinary medicinal product that is not in accordance with the SPC, including the misuse and serious abuse of the product.

The MAH should collect any available information on adverse events following off-label use related to his veterinary products. Reports of adverse events arising from off-label use should be routinely followed up to ensure that information is as complete as possible with regard to the clinical signs, treatment and outcome.

Reports of adverse events arising from off-label and/or cascade use may be obtained on veterinary products used outside the terms of the MA, e.g. use of a product in non-authorised species/indications, use at doses differing from those set out in the SPC and package leaflet. Such reports can provide useful information on the safety of the veterinary products and should be recorded by the person responsible for pharmacovigilance and reported to SFDA as other adverse events.

5.3. Requirements for reporting other pharmacovigilance issues

5.3.1. Reporting on investigation of the validity of the withdrawal period

Reports of such cases may arise from different sources including:

- Farmers or veterinarians detecting residues of Veterinary Products when testing bulk milk for antibiotics.
- Analytical laboratories or food producers who routinely monitor foodstuffs for residues, for example in slaughterhouses or dairies.
- State or regional authorities conducting residue surveillance on food from food producing animals.

Where levels of Veterinary Products residues in tissues or food products of treated food producing animals are above the established maximum residue levels while the recommended withdrawal period of the given Veterinary Products has been respected,

this information may cast doubt on the validity of the withdrawal period and consequently should be investigated and reported to SFDA.

Such reports should not normally be expedited (i.e. reported within 15 days after receipt), but should be discussed in the relevant PSUR (see Part I Chapter 6. Requirements for Periodic Safety Update Reports).

However, in certain specific circumstances, where these reports cast important doubt on the appropriateness of the recommended withdrawal period of the given Veterinary Products, the reports should be recorded and reported promptly to SFDA.

The report should contain details about:

- the source of the report,
- the Veterinary Products, including active ingredient(s),
- MA number and batch number if available,
- the route of administration,
- the withdrawal period applied,
- date of use,
- date of detection of the residues,
- the level of residues detected,
- the location of the case,
- the species,
- the analytical method used to determine the residues,
- any other information necessary for a detailed evaluation of the case, and
- the steps taken by the MAH to investigate the matter.

5.3.2. Reporting on potential environmental problems

A potential environmental problem is a situation where animals of non-target species, other animals, human beings or plants are suspected to be adversely affected through exposure to a Veterinary Products present in the environment (see also section 5.4.2 Adverse events involving an untreated animal exposed to a Veterinary Products via a treated animal).

Any suspected environmental problem related to a Veterinary Products exposure should be recorded by the MAH as soon as it comes to his knowledge.

The minimum requirements for any potential environmental problem to be recorded by the MAH and reported to SFDA are:

- the location,
- the animal or plant involved (as appropriate),
- the nature of the suspected environmental problem and
- the suspected product(s).

Reports of potential environmental problems arising from the use of the Veterinary Products should not normally be expedited (i.e. reported within 15 days after receipt), but should be discussed in the relevant PSUR (see Chapter 6. Requirements for Periodic Safety Update Reports). However, in certain specific circumstances, in order to limit further environmental damage and to evaluate the benefit-risk balance, reports of potential environmental problems related to the Veterinary Products should be reported.

5.4.Guidance on particular types of reports

5.4.1. Adverse events involving more than one species:

If more than one species is concerned in the same adverse event, separate reports should be submitted for each species, although it should be indicated that the reports are linked. This applies when more than one animal species is involved, or when an animal and a human being are involved.

5.4.2. Adverse events involving an untreated animal exposed to a Veterinary Products via a treated animal:

If an adverse event has occurred in an untreated animal exposed to a treated animal, even if of a different species, a single report should be submitted relating only to the animal which experienced the adverse event. In this case a short explanation should be included in the dose details to clearly indicate which animal (or animal species) was treated. In addition, the administration route details should reflect the route by which the affected animal was exposed, e.g. oral route if the contact was by licking or

grooming, cutaneous route if there was dermal contact between the treated and untreated animal.

5.4.3. Adverse events in offspring exposed through a parent

5.4.3.1. Spontaneous abortion or stillbirth

A report should be submitted relating only to the parent. The animal details should be those of the mother.

5.4.3.2. Adverse events in offspring only

If the offspring experienced an adverse event (e.g. malformation), while the parent was unaffected, a report should be submitted relating only to the offspring. If appropriate, the animal details should record the number of offspring in the litter which reacted. A short explanation should be included in the dose details and narrative to indicate which parent was treated. Information concerning the number of adult animals treated should be included in the case narrative to indicate what proportion of the flock or herd was affected. This is particularly important in cases of suspected lack of efficacy.

5.4.3.3. Adverse events in mother and offspring

In cases where the mother and offspring experienced one or more adverse events following the administration of a Veterinary Products to the mother during pregnancy resulting in in utero exposure of the foetus(es), a single report should be submitted relating to both mother and offspring. The animal details to be recorded should be those of the mother. The number of treated animals should be recorded as one animal. The number of offspring which reacted and the fact that their exposure occurred in utero should be recorded in the case narrative. The clinical terms used to describe the adverse event should include the clinical signs observed in the offspring as well as those experienced by the mother. A clinical term indicating the congenital nature of the adverse event should also be included. If the mother or any offspring died, the report should be sent as an expedited report.

5.5.Required information for adverse event reports

5.5.1. Minimum information for adverse event reports

For a recordable case the MAHs are expected to record all data relevant for the evaluation and provided by the sender or obtained in the context of the case, at least the minimum criteria. If relevant for the evaluation, the MAH is expected to follow-up the adverse events with reasonable effort, to obtain further pertinent information. It is essential for MAHs to provide details as completely as possible, including all relevant clinical information, in order to facilitate assessment. The original words and/or phrases used by the reporter should be provided even if they are also coded using the VeDDRA List of Clinical Terms for reporting adverse events in animals and humans (see Annex 2. References). The use of controlled terminology is a crucial factor in harmonising the exchange of pharmacovigilance information and the VeDDRA terminology is the most important of the standard lists. It is required that the MAH shall use the VeDDRA terminology.

Follow-up reports on incomplete adverse event reports should be submitted by the MAH, in particular in cases where only the minimum information was submitted or at least when the investigation of the adverse event is completed.

A report will be considered an acceptable and reportable adverse event report provided that at least the minimum information outlined below is available. These details should be recorded by the MAH for any adverse event, whether non-serious or serious, whether occurring in animals or in human beings.

Minimum information for adverse event reports:

1. An identifiable source. Wherever possible this should include the name and address of the primary reporter. Initials, geographic location or other unique identifier should be provided to allow the collection of further information and to avoid any duplication of reports.
2. Animal details: Species, sex, age. Patient details: Sex, age or adult/child. For both animal and human reports it should be stated if sex and/or age are not known.
3. Veterinary Products concerned (name and marketing authorisation number).
4. Adverse event details.

The electronic reporting forms contain additional data fields that are marked as mandatory.

Additional criteria to enable electronic reporting:

1. Report number
2. Receiver identifier
3. Date of the reaction. If this is not known, the closest approximation in terms of year (and month if known) should be substituted.
4. The number exposed/affected. If the number exposed is not known, the number affected should be substituted. If neither the numbers exposed nor affected are known, a notional figure should be used, which should be justified. If the exact numbers of animals exposed are not known, an estimation should always be provided. It is not acceptable to omit this information.

These details allow for the management and electronic distribution of adverse event reports, and assist in the detection of duplicate reports.

For adverse events for which deadlines for reporting apply, the reference point for deadlines for submission of reports is the time of receipt of the minimum information. It should be emphasised that these are minimum requirements and the MAH should consider and try to include, for each adverse event, information on the items in sections 5.5.2 MAH details and original reporter's details to 5.5.11 Human adverse reactions in order to facilitate a full evaluation.

5.5.2. MAH details and original reporter's details:

1. The name of the sender employed by the MAH.
2. Address, telephone and fax number of the sender.
3. MAH report reference number.
4. Date of receipt of report by MAH (any personnel of the MAH or an organisation having a contractual arrangement with the MAH).
5. Source of report, e.g. spontaneous, post-authorisation safety studies and clinical studies.
6. Details of the original reporter - name (if acceptable under national law), address, profession and specialty (if available).
7. Reporting country (country where the incident occurred).

8. Purchase country (where suspect product was purchased if different from that above).

5.5.3. Animal Details:

- Number treated.
- Characteristics of animals showing signs:
- Species.
- Breed.
- Sex.
- Age (in days/weeks/months/years).
- Weight (in kilograms).

5.5.4. Suspect veterinary medicinal product details:

1. Product name(s)/brand names(s).
2. Approved scientific name(s) (INN - International Non-proprietary Name).
3. Marketing authorisation number.
4. ATCvet code
5. Pharmaceutical form.
6. Batch number.
7. Expiry date of batch - if relevant.
8. Storage details - if relevant.

5.5.5. Treatment details:

1. The person who administered the veterinary products (e.g. animal owner, veterinary surgeon etc.).
2. Reason for treatment including diagnosis.
3. Dose (and frequency if relevant) of treatment given.
4. Route of administration.
5. Start date.
6. Stop date and/or duration of treatment.

7. Time between administration and adverse event.
8. Action taken after adverse event (e.g. removal of treatment with Veterinary Products, dose reduced).
9. Previous adverse event(s) to the Veterinary Products if occurred/reported, (re-challenge information) to include:
 - Approximate date when animal(s) previously treated with product.
 - Description of adverse reaction(s).
 - Outcome including any treatment given.

5.5.6. Other products used concurrently

All relevant medicinal treatment preceding the adverse event should be provided when available. This should also include non-prescription medicines, *ex tempore* (magistral) preparations and medicated feedings tuffs if applicable. In the case of *ex tempore* (magistral) preparations, details of individual constituents of the formula should be indicated.

For each medication:

1. Product name(s)/brand names(s).
2. Approved scientific name(s) (INN - International Non-proprietary Name).
3. MA number.
4. ATCvet code.
5. Pharmaceutical form.
6. Batch number if relevant.
7. Expiry date of batch - if relevant.
8. Storage details - if relevant.

Treatment details for other product(s) used concurrently:

1. The person who administered the veterinary products (e.g. animal owner, veterinary surgeon, etc.).
2. Dose (and frequency if relevant) of treatment given.
3. Route of administration.
4. Start date.

5. Stop date and/or duration of treatment.
6. Other relevant information.

5.5.7. Details of the animal adverse event(s):

The case narrative is very important and should contain all known relevant clinical and related information, including animal, exposure or treatment details not otherwise reported, course of adverse event(s) and description of the adverse event(s) including the outcome, diagnosis, and any other information that supports or negates an association between a product and an adverse reaction. The narrative should serve as a complete and comprehensive case report, presented in a logical time sequence, ideally in chronological order. The use of abbreviations and acronyms should be avoided.

1. Description of adverse event(s) including site and severity (intensity of the adverse event), and clinical signs.
2. Start date or onset of adverse event.
3. Stop date or duration of adverse event.
4. Specific treatments adopted against the observed adverse event.
5. Number of animals showing signs.
6. Number of animals dead.
7. De-challenge information (e.g. any obvious effect of removal of treatment).
8. If available, the following information should be provided:
 - Number of treated animals alive with sequelae.
 - Number of treated animals recovered.

5.5.8. Other information

Any other relevant information available to facilitate assessment of the case should be provided, such as disposition to allergy, changes in feeding habits, or effects on production parameters.

When pre-mixes, which have been incorporated in medicated feeding stuffs, are causing an adverse event in animals or human beings, both the pre-mix and the medicated feeding stuffs should be investigated without delay.

In addition to the standard reporting details, additional factors may need to be examined and reported. Additional important information includes the composition of the medicated feeding stuffs (with a particular focus on other medicated pre-mix(es)), the inclusion levels of active substances of the premix, the operation of the milling process(es), the possibility of cross contamination and, when possible, the estimated dosage administered to individual target animals. In addition, information on feed additives may be important, when available.

5.5.9. Investigation

In the event of a fatal outcome the cause of death should be provided and its relationship to the serious adverse event commented upon. Post-mortem examination findings and laboratory results should be provided if such tests were carried out. The nature of the MAH investigation should be described, and a summary of any analysis of product samples should be provided, if relevant.

5.5.10. Causality assessment

MAHs should comment on whether they consider there is a causal association between the suspected Veterinary Products(s) and adverse event(s) reported and should provide the criteria on which they have made the assessment.

The causality assessment should be carried out using the ABON system. According to this system, five categories of causality can be selected:

- Category A: Probable.
- Category B: Possible.
- Category O: Unclassifiable/Unassessable (events where insufficient information was available to draw any conclusion).
- Category O1: Inconclusive (events where other factors prevented a conclusion being drawn, but a product association could not be discounted).
- Category N: Unlikely to be product related.

In assessing causality, the following factors should be taken into account:

1. Associative connection, in time - including dechallenge and rechallenge following repeated administration (in clinical history) - or in anatomical sites.
2. Pharmacological explanation, blood levels, previous knowledge of the drug.
3. Presence of characteristic clinical or pathological phenomena.
4. Exclusion of other causes.
5. Completeness and reliability of the data in the case reports.
6. Quantitative measurement of the degree of contribution of a Veterinary Products to the development of an adverse event (dose-effect relationship).

For inclusion in category "A" (probable), it is recommended that all the following minimum criteria should be complied with:

- There should be a reasonable association in time between the administration of the Veterinary Products and onset and duration of the reported adverse event.
- The description of the clinical phenomena should be consistent with, or at least plausible, given
- The known pharmacology and toxicology of the product.
- There should be no other equally plausible explanation(s) of the case (if such are suggested, are they valid? What is their degree of certainty?). In particular, concurrent use of other veterinary products (and possible interactions) or intercurrent disease should be taken into account in the assessment.

Where any of the above criteria cannot be satisfied (due to conflicting data or lack of information) then such reports can only be classified as "B" (possible), "N" (unlikely), "O1" (inconclusive) or "O" (unclassifiable/unassessable).

For inclusion in category "B" (possible), it is recommended that this be applied when VETERINARY PRODUCTS causality is one (of other) possible and plausible causes for the described adverse event but where the data does not meet the criteria for inclusion in category "A".

For inclusion in category "O" (unclassifiable/unassessable), all cases where reliable data concerning an adverse event is unavailable or is insufficient to make an assessment of causality.

For inclusion in category "O1" (inconclusive), all cases where a veterinary products association cannot be discounted but other factors prevent a conclusion being drawn.

For inclusion in category "N" (unlikely), cases where sufficient information exists to establish beyond reasonable doubt that there is an alternative explanation to the adverse event that is not related to a veterinary product. Further guidance on how to carry out causality assessment is available in the veterinary Products Guideline on Harmonising the Approach to Causality Assessment for Adverse Reactions to Veterinary Medicinal Products (see Annex 2. References).

5.5.11. Human adverse reactions

Information about any human adverse reactions to veterinary products, whether occurring in conjunction with the treatment of animals, the handling of a veterinary products or following exposure through the environment, should be provided in accordance with this guidance. The minimum information required for a human adverse reaction report is outlined in section 5.5.1. The MAH should consider and try to include, for each human adverse reaction, information on the items below in order to facilitate a full evaluation. Asymptomatic human events should be recorded but not transmitted to SFDA

The case narrative is very important and should contain all known relevant information not otherwise reported, including how the exposure occurred, e.g. accidental or routine use, the degree of exposure e.g. the volume injected or splashed, the course of event(s), medical diagnosis, and any other information that supports or negates an association between a veterinary products and an adverse event. The narrative should serve as a complete and comprehensive case report, presented in a logical time sequence, ideally in chronological order. The use of abbreviations and acronyms should be avoided.

Information facilitating a full evaluation:

1. Patient identification (as appropriate according to national laws). A name or unique identifier should be provided to allow the collection of further information and to avoid any duplication of reports.
2. Sex.

3. Age, date of birth or adult/child.
4. Occupation/person status, if relevant to exposure to veterinary products, e.g. veterinary surgeon, farm worker, pet owner.
5. Date veterinary products used or date exposed to veterinary products(s).
6. Date of human adverse reaction.
7. Product details: Product/brand name, MA number, active substance and ATCvet code(s). This should be provided for each of the veterinary products to which the patient was exposed in the incident.
8. Nature of exposure, including type of exposure, e.g. inhalation, injection, ingestion or dermal, and duration.
9. Description of human adverse reaction including clinical signs and symptoms.
10. Outcome of human adverse reaction, e.g. extent of recovery, specific treatment required.
11. Name, address, telephone number of medical doctor/physician (or Poison Centre) if consulted.
12. MAH conclusions/comments on the human adverse reaction.
13. Animal and treatment data, e.g. method of administration, administration site, number and species of animals being treated.
14. Status (e.g. veterinarian, pharmacist, other health-care professional), name and contact details of the person who reported the human adverse reaction to the MAH, if other than the patient, and if acceptable under national law for the purposes of obtaining further information.

5.6. Reporting Time Frames

The MAH should transmit all adverse event reports requiring expedited reporting promptly and no later than 15 calendar days for serious adverse events and 72 hours for serious and unexpected adverse events from receipt. The date the MAH becomes aware of a report which fulfils the minimum information should be considered day 0.

The clock for expedited reporting starts (day 0) as soon as the minimum information has been brought to the attention of any personnel of the MAH or an organisation having a contractual arrangement with the MAH concerning conduct of pharmacovigilance.

5.7. Reports Published in Peer-reviewed Worldwide Literature

Adverse event reports from peer-reviewed worldwide literature are considered to be reports of which the MAH can reasonably be expected to be aware and have knowledge. The MAH is therefore expected to maintain awareness of possible publications. Adverse events from the scientific and veterinary literature should be reviewed to identify individual events which might qualify for reporting.

The MAH should report published adverse events associated with the use of its veterinary products in accordance with the requirements for adverse event reporting and in PSURs.

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 events described in the worldwide scientific literature to ensure that the MAH can comply with their reporting obligations.

5.8. Reports from Other Sources

If a MAH becomes aware of an adverse event report from sources other than those mentioned above, e.g. the lay press or other media, reasonable attempt should be made to obtain the minimum information that constitutes an individual adverse event and to follow-up the report.

5.9. Method of Reporting

Electronic reporting of adverse events is mandatory, save in exceptional circumstances.

The available electronic reporting solutions and the procedural steps for all partners are explained in Part II.

All possible data fields for reporting to SFDA are described in detail in the Guideline on data elements for the electronic submission of adverse reaction reports related to veterinary products.

Where there are no appropriate fields in which to record specific details, the information

should be provided in the case narrative or as attachments, as appropriate.

5.10. Signal Detection

One of the aims of pharmacovigilance is the detection of new safety signals in relation to the use of veterinary products. A signal should be considered as information reported on a possible causal relationship between an adverse event and a veterinary product, the relationship being unknown or previously incompletely documented.

The regular review and analysis of adverse events in a pre-defined time period for one specific veterinary products in one particular species might lead to the identification of potential signals when, for example:

- an increase in the number of adverse events in a short period is observed,
- an increase in the frequency of a particular clinical sign is recorded, compared with the expected frequency for that sign,
- new unidentified clinical signs are highlighted,
- a potential impact on public or animal health is suspected.

In the case of an increase in the number of adverse events, investigations should be carried out to clarify whether or not such findings could be considered as “normal”, in order to take appropriate measures.

In the case of signal detection of particular clinical signs, it might be useful to compare the number of citations of such clinical signs either with the number of other clinical signs recorded for the particular veterinary products, or with the number of the same clinical signs recorded for other veterinary products.

5.11. Urgent Safety Restrictions

Urgent safety restrictions may be taken in the event of a risk to human or animal health or to an urgent safety restriction is an interim change to the product information due to new information having a bearing on the safe use of the medicinal product, concerning in particular one or more of the following items in the SPC: therapeutic indications, posology, contraindications, warnings, target species, and withdrawal periods.

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

Reporting requirements remain following suspension of the MA of a veterinary product (see Part I Chapter 5. Adverse Event Reporting and Chapter 6. Requirements for Periodic Safety Update Reports).

Where an MA is withdrawn or revoked, the former MAH is encouraged to continue to report in line with Part I Chapter 5. Adverse Event Reporting to, for example, facilitate review of delayed onset adverse events and retrospectively notified cases. It may be appropriate to continue submission of PSURs after withdrawal or revocation of the marketing authorisation. This should be addressed and agreed on a case-by-case basis with the SFDA.

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 veterinary product to SFDA at defined time points post-authorisation. At these times, MAHs are expected to provide succinct summary information on all adverse events together with a critical evaluation of the benefit-risk balance of the veterinary products in the light of any new or changing pharmacovigilance information.

This evaluation is necessary to ascertain whether further investigations need to be carried out and/or whether changes should be made to the SPC or other product information. Each PSUR reporting period is defined by a Data Lock Point (DLP). The DLP is the date designated as the cut-off date for data to be included into a particular PSUR. On this date the data available to the author of the PSUR is extracted for review and stored. More information for setting the DLP is given further below.

This Chapter is consistent with VICH Topic GL 29 “Pharmacovigilance of Veterinary Medicinal

Products – Management of Periodic Summary Update Reports (PSURs)” (see Annex 2. References).

The requirement for the submission of a PSUR applies irrespective of whether the veterinary products is marketed or not, however in certain circumstances an abridged PSUR is considered sufficient (see Chapter 6.3.2 Content of Periodic Safety Update Reports – Non-marketed products) Submission of electronic copies of signed PSURs (e.g. portable document format, pdf) is strongly encouraged.

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, providing a basis for conclusion whether further investigations or changes in the SPC will be necessary.

For this purpose, the PSUR should include information on the following types of adverse event reports /case histories received during the period of review:

- All adverse events in animals and in human beings, sent spontaneously to the MAH
- Any suspected transmission of an infectious agent via a veterinary product.
- Serious and non-serious adverse event reports from post-authorisation safety studies (see Chapter 7 Company-Sponsored Post-Authorisation Safety Studies).
- Any available information on investigation of the validity of a withdrawal period or any potential environmental problems, caused by the product under the normal conditions of use.
- Any available information on investigation of adverse events related to off-label use.
- Any available information on lack of expected efficacy, as specifically for veterinary products used in the treatment of life-threatening conditions and for certain other veterinary products, e.g. antibiotics or vaccines, lack of expected efficacy may represent a significant hazard and in that sense may give rise to a safety concern.
- Any data from previously requested close monitoring.

6.2.2 Frequency and timing of Periodic Safety Update Reports

6.2.2.1 Submission of PSURs

It is strongly recommended that, before submitting the PSUR, the MAH should make sure that all reports from the line listings have been submitted electronically (without duplicate reporting) as described in Part II: Guidelines for Marketing Authorisation Holders on Electronic Exchange of Pharmacovigilance Information.

The periodicity for submission of PSURs is established in Article 5 (9) of the GCC veterinary products executive regulation (see Annex 2. References). PSURs shall be prepared immediately upon request or at least every six months after authorisation until the placing on the market.

Following the initial placing on the market, PSURs shall be submitted

- immediately upon request, or at least at the following intervals:
 - 6-monthly for the first 2 years,
 - annually for the subsequent 2 years, and
 - thereafter, at three-yearly intervals.

The PSUR cycle should be based on the Saudi Birth Date (SBD, date of the first marketing authorization within the Saudi Arabia) of a veterinary products or its International Birth Date (IBD, date of the first marketing authorisation for a same or similar product granted anywhere in the VICH region).

Once a veterinary product is authorised in Saudi Arabia, even if it is not marketed, the MAH is required to submit PSURs at 6-monthly intervals, until initial placing of the veterinary product on the market. When launch dates are planned, this information should be reflected in the forthcoming PSUR.

The PSUR covering this period during which the product is launched is considered the last of the six month PSURs to be submitted before 'initial placing on Saudi market'.

After this 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 DLP according to the SBD or IBD.

In the light of experience gained with the operation of veterinary pharmacovigilance, requirements for PSUR reporting frequency might be amended by Comitology procedures.

6.2.2.2 PSUR Reporting Period

Each PSUR should cover the period of time since the last PSUR and should be submitted within 60 days after the DLP. Gaps and overlapping of data should be avoided.

DLPs should be set according to the Saudi Birth Date (SBD, date of the first marketing authorization within the Saudi Arabia) of a veterinary products or its International Birth Date (IBD, date of the first marketing authorisation for a same or similar product granted anywhere in the VICH region).

Preparation of PSURs according to the International Birth Date:

Veterinary products which are also authorised outside the Saudi, will have an IBD. This is the date of the first marketing authorisation for a same or similar product granted anywhere in the VICH region. For veterinary products first authorised in the Saudi Arabia, the SBD is the IBD. For administrative convenience, if desired by the MAH, the IBD may be designated as the last day of the same month.

In order to harmonise PSURs internationally, the MAH may use the IBD to determine the DLPs in Saudi. If the IBD is used, the first DLP must be within 6 months of the SBD, unless other requirements have been laid down at the time of granting the MA. Regardless of whether the IBD is used, the PSUR should be submitted within the 60 days following the DLP, taking into account that the date of submission of the PSUR is in compliance with the stipulated submission schedule. For the purpose of the PSUR the relevant dataset should be locked at the DLPs and, as relevant, extracted from the database for analysis (frozen) in relation to the product. Up-to-date safety data, i.e. data that becomes known to the MAH after the DLP and which may influence the evaluation should also be included in the PSUR (see Part I section 6.3.1.10).

The PSUR should cover all authorised presentations covering all pharmaceutical forms and target species, whether authorised with the initial MA or at a later time point, e.g. through an extension of the MA. For each subsequent variation to the initial MA it will be decided on a case-by-case basis, as justified on basis of important safety concerns, whether the submission cycle for the PSUR needs to be changed. The DLPs remain based on the date of the initial MA.

There may be situations where exceptionally, as justified on basis of important safety concerns, the submission of 6-monthly and subsequent yearly PSURs may be re-started, or where other amendments of the periodicity are required by SFDA or applied for by MAHs.

6.3. Content of Periodic Safety Update Reports

For veterinary products authorised by SFDA the PSUR should be written in English.

The reaction terms used in the PSUR should be in accordance with the VeDDRA terminology (see Annex 2. References). However, when the original reporter's terms are not medically appropriate or meaningful, the MAH should use the best alternative compatible event terms from VeDDRA to ensure the most accurate representation possible of the original terms.

The structure of a PSUR should follow the guidance given in section 6.3.1 Content of Periodic Safety Update Reports – Marketed Products. For non-marketed products without any reports of adverse events an abridged PSUR is considered sufficient (see section 6.3.2 Content of Periodic Safety Update Reports – Non-marketed products).

6.3.1. Content of Periodic Safety Update Reports – Marketed Product

For marketed veterinary products the PSUR should fulfil the following format and content:

6.3.1.1. MAH and product details

Each PSUR should include:

- i) The name of the MAH
- ii) The veterinary product name(s)
- iii) The MA number(s)
- iv) Procedure number, if applicable
- v) SBD-IBD / Start date for PSUR-submission cycle
- vi) The period covered by the PSUR
- vii) Chronological order of PSUR (e.g. 1st 6 month PSUR after initial placing on the market)

6.3.1.2. Update on regulatory or MAH actions taken for safety reasons

An overview of regulatory and MAH actions taken anywhere in the world for safety reasons (e.g. follow-up measures, specific obligations and variations) since the last period covered in the PSUR indicating scope, status and date should be given. Significant changes in the wording of the SPC should be explained, where of relevance to safety.

6.3.1.3. Summary of Product Characteristics (SPC)

The latest version of the relevant SPC must be included for reference in the report. It is recommended that when the SPC changed significantly in matters relevant to safety during the covered period, the nature of the change(s) should be succinctly explained in the PSUR. If evaluation of safety data leads to any proposed changes in the SPC.

6.3.1.4. Estimations of exposure

Sales volume

Each PSUR should contain the number of doses/amount of veterinary products sold within the reporting period in Saudi Arabia and worldwide. The sales information should be expressed per presentation in an appropriate form. The following forms are suggested:

- Vaccines to be expressed in numbers of doses;
- Liquid to be expressed in litres;
- Powder to be expressed in kilograms;
- Tablets to be expressed in numbers of tablets;
- Sprays to be expressed in litres or kilograms;
- Collars to be expressed in numbers of collars;
- Paste to be expressed in kilograms
- Pipettes for spot-on solution to be expressed in numbers of pipettes.

Number of animals treated

The number of animals treated should be calculated independently of reported adverse events. When calculating the number of animals treated during a period, the following points should be taken into consideration:

- For some veterinary products the number of doses (individual units) sold is equivalent to the number of animals treated (e.g. anthelmintic boli, flea collars).

For veterinary products formulated as pastes, aerosols, eye/ear preparations or other formulations where it is likely that each unit of veterinary products (for example, syringe, single dose pipettes) will be dispensed for the treatment of an individual animal, the number of individual units sold should be considered equivalent to the number of animals treated.

- For the majority of pharmaceutical veterinary products, the number of animals treated will be a function of:
 - Authorised treatment regimen (daily dose (mg/kg) x duration of treatment (days)) as detailed on the authorised SPC. Where a range for dose or duration of therapy is indicated on the SPC, it is appropriate to calculate incidence based on maximum recommended exposure (that is, use the upper limit of the dose range and/or longest duration of treatment). Following from the calculation of maximum exposure, it is acceptable to propose alternative assessments of incidence based on known conditions of use of the product. Any such alternative calculations should be justified. For veterinary products indicated for continuous (life-long) treatment, a standard duration of treatment should be established and any interval should be justified by the MAH.
 - Amount of veterinary products sold
 - Average weight of target population (kg). The chosen average weight is to be justified.

Standard weights are recommended in the table below and use of any other standard weight, including for those species not listed below, should be justified in the PSUR.

Exposure in pigeons is recommended to be calculated on basis of 30 pigeons/litre of drinking water.

Species and subpopulations	Standard weight (kg)
horse	550
dog	20
cat	5
cow	550

beef calf	150
camel	600
Camel calf	180
newborn calf (camel and cow)	50
sheep	60
lamb	10
poultry, broiler	1
poultry, layer hen	2
poultry, turkey	10
rabbit	1.5

- It is expected that the values used for estimation of the number of animals treated would be representative of the conditions of use of the veterinary products. For veterinary products authorised for more than one species it is difficult to calculate individual species' exposure. However, it is suggested to estimate the number of animals treated for all authorised species individually using the estimated conditions of use of the veterinary products (sales/species). Additional information to explain how the distribution of proportional use in different species is estimated should be provided.
- For immunological veterinary products, the number of animals treated may be considered equivalent to the total number of doses sold. Any calculations should take into account the recommended treatment regimen (initial course plus booster doses).

6.3.1.5. Incidence of Adverse Events

A PSUR must address the relationship between the sales volume of a veterinary products and the numbers of adverse events reported.

An overall incidence should be calculated for all spontaneous adverse reactions (A, B, O, including O1) that occur after recommended or non-recommended (off-label) use in the target species. For clarity, adverse reactions from post-authorisation safety studies should be excluded.

In this respect the use of a veterinary products in non-authorised species under specific conditions

A proportion of veterinary products is indicated for more than one target animal species. Where this situation pertains it is recognised that it is difficult to calculate individual species incidence of adverse events.

However, it is suggested that in addition to the ratio of all animals expressing an event the ratio be computed for each species based on the estimated conditions of use of the veterinary products (sales/species) (see 6.3.1.4).

For the calculation of incidence of adverse reactions, it is suggested that MAHs adopt the following two-tier approach:

Calculation 1 – Ratio of animals expressing an adverse event

In the first instance, the ratio of the number of animals expressing an adverse event (reports assigned a causality code of A, B or O, including O1, N) during a period to the amount of veterinary products sold during that period should be computed:

$$\text{Ratio of animals with adverse event} = \frac{\text{No of animals with adverse event during period}}{\text{No of doses sold during the period}}$$

This calculation is based on data that tends to be accurate and can be used reliably to monitor trends from one PSUR to the next. Any increase in this ratio relative to previous PSURs may signal a problem and the need for more detailed evaluation of the pharmacovigilance data.

For PSURs covering 3 years, sales volume should be broken down by calendar year and the ratio of the number of animals with adverse event to the amount of veterinary products sold should be computed for each of the years concerned by the report.

Calculation 2 – Incidence

The incidence (%) of adverse reactions (reports of adverse events assigned a causality code of A, B or O, including O1) should be calculated by dividing the total number of animals reacting during the period by an estimate of the number of animals treated during the period of the report and multiplying by 100.

$$\% \text{ Incidence} = \frac{\text{No of animals reacting during period} \times 100}{\text{Estimated No of animals treated during the period}}$$

This calculation may then be revised to exclude O and O1 coded reports (that is, this calculation would focus on A-probable - and B-possible -coded reports only).

The values included in the calculation of incidence must be justified. It is expected that the values used for estimation of the number of animals treated would be representative of the conditions of use of the veterinary products. All assumptions used for calculation should explicitly be stated.

6.3.1.6. Data review

The report should include a data review based on the MAHs analysis (including causality assessment) of the individual adverse events reported during the period concerned by the PSUR.

The analysis of the adverse events reported should be supported by tables or tabulations summarizing the main findings. It may be helpful, especially for PSURs which contain a large number of adverse events, to introduce summary tabulations and prepare separate tables e.g. for serious expected reactions, serious unexpected reactions, non-serious unlisted reactions (not mentioned in the SPC), or on basis of VeDDRA categories on organ level (e.g. System Organ Class (SOC) or Preferred Term (PT) level).

The data review should be structured as follows:

- Adverse events in target species, including events of suspected lack of expected efficacy and those events occurring after off-label use in target species and
- Adverse events reported in humans
- Other pharmacovigilance fields:
 - Adverse events after use in non-target species

- Potential environmental problems arising from the use of the veterinary products
- Investigations of the validity of the withdrawal period
- Transmission of any infectious agent via a veterinary medicinal product

Information on the individual adverse event reports should be presented as line listings. The main focus in the data review should be the presentation, analysis and evaluation of new or changing safety data received during the period covered by the PSUR (e.g. evidence of previously unidentified toxicity or safety concerns, increased frequency of expected undesirable effects or known toxicity).

It is necessary to structure the data review further in relation to e.g. different formulations (dosage form(s) and strength(s)), target species (if the veterinary medicinal product is authorised for use in more than one species), event type (that is, serious, non-serious, human adverse event, etc.), and country where the event occurred. Aspects relevant to different batches of immunological products should be considered in the PSUR when relevant, and batch numbers should be identified in the review and the line listings, as available.

6.3.1.7. Non-spontaneous Reports

A narrative overview of available data from other sources (e.g. post-authorisation safety studies, published adverse event reports, user experience studies) should be included in this section. The data should be analysed and discussed as part of the benefit-risk assessment.

The overview should include a review of all adverse event reports eligible for expedited reporting that were received during the PSUR period from post-authorisation safety studies. For guidance on progress reports for post-authorisation safety studies, see Part I Section 7.6 Liaison with regulatory authorities and reporting.

Summaries from post-authorisation safety studies should be included once final results become available, and should consider all adverse events reported from the study.

A bibliographic listing of the scientific articles that address adverse events and which are found in a widely accepted search engine published during the PSUR period that pertains

to the veterinary products should be included as an appendix. Information on databases used should be provided. The literature search should primarily be product-based.

Additionally, a bibliographic line listing of the studies that address adverse events and for which the MAH is the sponsor, should be included as an appendix.

6.3.1.8. Other Information

Adverse events arising from prescription errors or medication errors, including those due to invented names of veterinary products or similar appearance (e.g. mix-up with another veterinary products) should be reported in PSURs.

Where names convey misleading therapeutic connotations, there may be a risk for misuse or abuse of the product. Adverse events arising from such misuse or abuse should be reported in PSURs.

A summary report on medication errors, including those due to name confusion, occurring with the veterinary products should be submitted as an annex to the PSUR.

6.3.1.9. Overall Safety Evaluation

Together with concise summary information on all adverse events, the PSUR should include a scientific analysis of the data presented and a critical evaluation of the benefit-risk balance of the product in light of any new or changing pharmacovigilance information, written by a suitably qualified expert for pharmacovigilance. It should clearly be stated, whether further investigations will be necessary and whether the wording of the SPC needs to be changed.

This section should include (lack of significant new information should be mentioned for each):

- information on any previous action taken by either regulatory authorities or the MAH as a result of safety issues, and
- any new important information on the following:
 - i) evidence of previously unidentified toxicity or safety concerns
 - ii) increased frequency of known toxicity or expected undesirable effects
 - iii) drug interactions

- iv) adverse events in animals associated with off-label use, including overdose and its treatment
- v) human adverse reactions related to the use of the product
- vi) lack of efficacy
- prescription errors/medication errors, including those associated with invented names or with the presentation of the veterinary products, that have safety implications, if available.
- information on investigation regarding the validity of withdrawal periods arising from the use of the veterinary products
- any environmental issues, caused by the veterinary products under normal conditions of use
- any urgent safety issues that occurred during the period covered.

The evaluation should in particular:

- indicate whether the safety information remain in line with the cumulative experience to date and the SPC or whether changes should be made to the SPC or other product information, and
- ascertain whether further investigations need to be carried out, and
- specify any action recommended and the reasons why.

The overall safety evaluation should primarily be organised by VeDDRA System Organ Class (SOC) – terminology rather than by categories like serious/non-serious or known reactions/new reactions; 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.

An increase in the frequency of reports for known adverse events 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 events or in the

safety profile and whether an explanation can be proposed for such a change (e.g. species or number of animals exposed, duration of exposure).

6.3.1.10. Important information received after Data Lock Point

This section is for reporting any important new information received by the MAH since the dataset was locked for review. It may include significant new cases or follow-up data that affect the interpretation or evaluation of existing reports. The impact of this information on the overall safety evaluation should be discussed.

MAHs are reminded that the respective data relating to serious adverse events in animals or human adverse reactions obtained after the DLP must also be reported expedited to SFDA as expedited reports as described in section 5.2 Requirements for expedited reporting.

6.3.1.11. PSUR line listings

The minimum information constituting a reportable adverse event is listed in section 5.5 Required information for adverse event reports.

All individual reports (A, B, O, O1 and N coded reports) should be presented as line listings.

Expedited reports received during the PSUR reporting period from post-authorisation safety studies should be included in the line listing. See also Part I Section 7.6 Liaison with regulatory authorities and reporting.

In order to relate the data review to the line listings, it is necessary to separate data e.g. relating to different formulations (dosage form(s) and strength(s)), target species (if the veterinary product is authorised for use in more than one species), reaction type (that is, serious, non-serious, human adverse event, etc.), and the country where the event occurred.

The standard information required in the line listing of a PSUR for adverse events in animals includes:

- i) MAH report reference number (country code (country where occurring))
- ii) Date(s) of treatment(s)/Date(s) of vaccination(s)

- iii) Were the veterinary products used as recommended?
- iv) Date of adverse event
- v) Number of animals treated
- vi) Species
- vii) Age(s)
- viii) Number of animals reacted (approximate)
- ix) Number of animal's dead
- x) Other products, including authorised medicated premixes, used concurrently (Trade name and active substances)
- xi) Presenting signs/diagnosis, including timing and duration
- xii) VeDDRA terminology (for description of signs/diagnosis)
- xiii) MA comments – brief, informative narrative
- xiv) Causality assessment (A, B, O, O1, N code)

The standard information required in the PSUR for human adverse reactions related to the use of a VMP includes:

- a) MAH report reference number (country code (country where occurring
- b) Date(s) of exposure
- c) Date(s) of human reaction
- d) Name(s) and region of address (for cross-reference to avoid duplication)
- e) Occupation
- f) Nature of accident/exposure
- g) Nature of human reaction/symptoms
- h) Outcome of human reaction
- i) MAH comments – brief, informative narrative

6.3.2. Content of Periodic Safety Update Reports – Non-marketed products

For authorised veterinary products that are not marketed or distributed anywhere and for which no adverse events (either in animals or in human beings) were observed in any additional trial (e.g. clinical trial, postauthorisation safety study) abridged PSURs are considered sufficient, which should contain the following elements only:

- trade name of the veterinary products
- marketing authorisation number(s) of the veterinary products,
- name and address of the MAH,
- date of SBD/IBD
- chronological order of the PSUR (e.g. 1st 6 monthly PSUR before initial placing on the market)
- a declaration of the MAH's QPPV, that as the veterinary products was not marketed or distributed anywhere in the world during the reporting period and as no adverse event (either in animals or in human beings) was observed in any additional trial (e.g. clinical trial, post-authorisation safety study), the benefit-risk balance afforded by the veterinary products has not changed since the date of the MA.
- estimated date for initially placing the product on the market.

6.4.Further guidance on submission and contents of Periodic Safety Update Reports in special situations

6.4.1. Submission of documents related to safety for Renewal of Marketing Authorisations

As part of the renewal application documents related to safety, the MAH needs to prepare or submit a PSUR Summary Bridging Report which is supported, if needed, either by

- a PSUR Addendum Report, or
- one PSUR in circumstances where the PSUR submission schedule is in synchrony with the renewal submission schedule.

6.4.1.1. PSUR Summary Bridging Report

For the purpose of the renewal application, the MAH should submit a PSUR Summary Bridging

Report, bridging all previously submitted PSURs. If, however, a PSUR covering the period since authorisation or last renewal is due at the time of submission of the renewal application, the PSUR replaces the need for a PSUR Summary Bridging Report.

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.

The PSUR Summary Bridging Report should not contain any new data but should provide a succinct summary, bridging and summarising previously submitted consecutive PSURs. A Summary Bridging Report should contain the following for the period covered by all previously submitted PSURs:

- Introduction (a brief description of the purpose of the document specifying the time periods covered and cross-referencing any referenced PSURs);
- Worldwide marketing authorisation status (number of countries which have approved the product);
- An overview of regulatory authority or MAH-initiated actions for safety reasons (an integrated summary of actions taken anywhere in the world if appropriate);
- An overview of changes (proposed or completed) to the SPC and package leaflet, to the Reference Safety Information Document (if applicable), based on pharmacovigilance grounds (significant changes over the entire period);
- An overview of exposure data (estimation of the total number of animals exposed in the time period) as well as incidence data and overview of human reactions;
- An overview of individual reports (brief statement outlining the total number of reports 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 may be appropriate to include summary tabulation for the types of reports of concern presenting adverse events, pointing out any differences from prior tabulations. In this case, there should be a clear understanding that the tables should be generated from live databases, which change over time as reports 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 report/event counts in these summary tables may differ somewhat from the contents of the individual tables in the PSURs. A general statement describing the differences should be provided;
- An overview of studies (a brief summary of important targeted post-authorisation safety studies);

- An overview of the reported information related to investigations of insufficient withdrawal period arising from the use of the veterinary products, lack of expected efficacy, adverse events related to off label use or any potential environmental problems;
- Other information (only highly significant safety information received after the DLP);
- Overview of the safety concerns and conclusion (unresolved key issues).

In addition, the Summary Bridging Report should also contain information highlighting any significant differences between the approved SPC and the proposed SPC.

Depending on the length of time and amount of safety data between the DLP of the previous PSUR and the renewal application, it may become necessary to provide an Addendum Report to the PSUR Summary Bridging Report.

6.4.1.2. PSUR Addendum Report for renewals

A PSUR Addendum Report is an update to the most recently completed PSUR when a safety update is required outside the usual SBD - or IBD - based PSUR submission schedule for a renewal application.

Because the renewal is an independent process, a PSUR Addendum Report does not change the submission schedule for PSURs nor has it influence on the DLPs of PSURs, as its content will be part of the following regular PSUR. The Addendum Report should summarise the safety data received between the DLP of the most recent PSUR and the date 60 days prior to the renewal application submission date, or a date as agreed with SFDA.

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 or requested 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 a 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 sections of the SPC relevant to pharmacovigilance (including a copy of the most recent 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).

6.4.2. Synchronisation of PSUR submission

The periodicity of PSUR submission may be amended, as required for any veterinary products by SFDA, or proposed by the MAH for nationally authorised products. This may result in more or less frequent submission of PSURs. For any veterinary products submission of PSURs on a period off more/less than every 3 years is not possible.

Where an amendment is proposed, the Applicant/MAH should submit, as part of the application, a reasoned request for the amendment, which, if granted, becomes part of the conditions of authorisation. For the MAH shortening a reporting period by submitting the PSUR earlier (e.g. for synchronisation of PSUR submissions) is always possible. If a MAH proposes a prolongation of the reporting period and thus later submission of the PSUR following authorisation he shall apply for this amendment, which should be supported by reasoned argument.

For newly authorised generic veterinary products application for submission of PSURs on a 3-yearly basis may be included in the MAA. PSURs for such products should preferably have the same DLPs as the corresponding originator product. Such applications will be assessed on a case-by-case basis by SFDA.

6.4.3. 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 veterinary products

safety, and to indicate whether changes should be made to the product information. Reference information is needed to carry out this comparison. Having one reference safety information document would facilitate a practical, efficient and consistent approach to safety evaluation and make the PSUR a unique report also accepted in other regions of the world.

It is recommended for MAHs participating in this initiative to prepare a Core Safety Data Sheet (CSDS) written in English, which consists of an extract of the core safety sections from the SPCs of the veterinary products for which the synchronised PSUR is submitted. The MAH should indicate in the PSUR which changes, amendments or modifications to this document are considered necessary on the basis of the data evaluated in the PSUR.

The CSDS is strongly encouraged to be submitted in addition to the regularly enclosed SPCs of all veterinary products for which the synchronised PSUR is prepared.

The Reference Safety Information to be used for PSURs for generic veterinary products based on SBD-IBD should consist of the common safety information that is included in all current SPCs of the concerned generic veterinary products as authorised at the time of the DLP. 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 CSDS in use are considered necessary on the basis of the data evaluated in the PSUR.

7. COMPANY-SPONSORED POST-AUTHORISATION SAFETY STUDIES

7.1. Introduction

Post-authorisation safety studies are pharmacoepidemiological studies or clinical studies carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised veterinary products.

This guidance applies to the conduct of post-authorisation safety studies that primarily evaluate the safety of marketed veterinary products when sponsored to any extent by the MAH. The guidance applies to studies where the veterinary products is provided by the MAH and to studies

where it is prescribed and used in the normal conditions of clinical veterinary practice when other forms of sponsoring by the MAH apply.

The study should be designed on a case by case basis for particular veterinary products and risks.

This Chapter defines the essential principles to be applied in a variety of situations.

It may become necessary to undertake a continuous surveillance of the veterinary products under field conditions for a defined period of time after the MA is granted.

Post-authorisation safety studies provide additional information on the risks of a veterinary products resulting in possible safety concerns being identified which may influence the overall benefit-risk ratio of the veterinary products. As a result, the SFDA may request, or the MAH may propose appropriate measures of risk prevention or propose studies to further investigate the risk and frequency of its occurrence. Such studies should comply with this guideline.

SFDA shall state the reasons for the request. The MAH shall collate and assess the data collected and submit it to SFDA for evaluation. Such studies should also comply with this guideline.

Post-authorisation safety studies should complement spontaneous reporting programmes. Spontaneous reporting programmes are important in the detection of signals, which might indicate a safety concern. However spontaneous reporting systems do not provide a quantitative risk assessment i.e. give the incidence of an adverse reaction in a population. Therefore, it is difficult to estimate the relevance of an adverse event described in single reports, without knowing the number of exposed and treated animals within a given time period. Post-authorisation safety studies can provide a denominator and give the answer to specific questions, which have been generated by signals from the spontaneous reporting system.

A commitment to post-authorisation safety studies may be required at the time of MA. In this case the study should be carried out on the basis of information of the SPC and in accordance with existing standards for the planning, conduct, reporting and archival of studies, such as in guidance on veterinary Good Clinical Practice (see Annex 2. References).

The basic types of questions to be addressed in post-authorisation safety studies are:

- long term effects that manifest themselves only after long periods of use, or after long periods of latency,
- low frequency specific effects – effects that can only be detected in large populations,

- uncertainty as to the clinical relevance of a harmful finding observed in pre-clinical studies in animals;
- efficacy in clinical practice, for the confirmation of lack of efficacy
- modifiers of efficacy: concurrent drugs, disease severity, husbandry conditions, feed,
- increase in frequency or severity of known adverse reactions,
- user safety aspects.

Monitoring of resistance to veterinary products investigations on the validity of withdrawal periods or surveillance of possible environmental problems under normal conditions of use might also be an objective of a post-authorisation safety study. Additional scientific guidance may be available for investigation of such specific topics.

7.2. Definition of a post-authorisation safety study

Post-authorisation safety studies are pharmacoepidemiological studies or clinical studies carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised veterinary products.

A post-authorisation safety study is any study of a marketed veterinary products sponsored by the MAH, which has the evaluation of clinical safety as a primary objective.

This guidance relates principally to those studies that primarily investigate a safety concern and/or when the number of animals can be justified in view of the expected increase in the knowledge of the safety of the product(s).

Clinical trials for new indications, new methods of administration or new combinations, are therefore excluded from the scope of this guidance.

7.3. Extent and objectives of post-authorisation safety studies

Post-authorisation safety studies may be conducted for the purpose of confirmation of previously undetermined safety issues (hypothesis generation), investigating risks (hypothesis testing in order to substantiate a causal association) or confirming the expected safety profile of a veterinary products under marketed conditions. They may also be conducted to quantify established adverse reactions and to identify risk factors.

Objectives may be:

- to measure the incidence of an adverse event in animals treated with the suspected veterinary products,
- to compare the incidence of an adverse event in animals treated and not treated with the veterinary products,
- to identify the risk factors associated with the development of an adverse event in animals treated with the suspected veterinary products, such as concurrent medications, disease severity, husbandry conditions, breeds, age, feed, etc,
- to identify risk factors responsible for an increased frequency or severity,
- to further clarify biological effects of adverse events due to a suspected veterinary product

The design to be used will depend on the objectives of the study, which must be 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.

7.4. Design of studies

Several different types of possible study designs may be applied to post-authorisation safety studies, e.g.

- Cohort studies, to provide information about the incidence of an event in a primarily unaffected population group,
- Case control studies, for hypothesis testing in a relatively short time at low cost, usually in retrospect,
- Group surveillance, study groups of animals where problems may arise which could be product related and to ascertain veterinary products exposure, or
- Clinical studies

7.5. Conduct of studies

Responsibility for the conduct of the study shall be vested in the sponsoring MAH and should be conducted in accordance with appropriate standards, e.g. Good Clinical Practice.

7.6. Liaison with regulatory authorities and reporting

MAHs proposing or requested by SFDA to perform a post-authorisation safety study are advised to discuss the draft protocol at an early stage with the SFDA. National legislative requirements or guidelines should be taken into account where these exist.

The company is strongly recommended to submit the protocol as well as any proposed communications to veterinarians or other investigators as well as to owners or animal handlers participating in the study, in addition to other relevant information, to SFDA in good time before the planned start of the study. The SFDA may comment as necessary. The responsibility for the conduct of the study will, however rest with the MAH.

The MAH should communicate with the SFDA, as requested in accordance with national legislation or other agreements, when the study has commenced and will normally provide a report on the progress at regular intervals and in PSURs or as requested by SFDA.

Recommendations for the content of a progress report for post-authorisation safety studies conducted in animals is presented below. For other types of studies, the progress report contents should be agreed with the SFDA.

i) Summary tables indicating the number of animals:

- identified as suitable for the study,
- entered,
- treated with study products;
 - treated with the authorised (investigational) product(s),
 - treated with other (control) product(s), including placebo,
- completed the study (followed up), or
- lost to follow up,
 - alive or unknown
 - died.

ii) Tabulation of the reasons for stopping treatment during the study

iii) Individual listing of causes for each death

iv) Table of all serious adverse events in animals eligible for expedited reporting and all human adverse reactions

- v) Line listing of all serious adverse events in animals eligible for expedited reporting and all human adverse reactions

Generally, only the data listed above should be included in the progress report. Other information should not be included without prior discussion with the SFDA. After review of the report SFDA may request additional information.

Other recommendations for progress reporting may have been given by SFDA.

The reporting requirements for reporting of serious adverse events in animals and human adverse reactions apply. All non-serious adverse events should be summarised in the final report.

A final report on the study should be sent to the SFDA within a pre-defined time frame.

Final results should be summarised and a summary of all adverse events provided in the next PSUR after final results become available.

8. OVERALL PHARMACOVIGILANCE EVALUATION AND SAFETY-RELATED REGULATORY ACTION

8.1. Introduction

The MAH and the SFDA must keep up to date with all relevant information in order to fulfil the following responsibilities:

- ensuring that all sources of information are screened regularly to identify potential signals;
- ensuring that appropriate action is taken in response to new evidence which impacts on the benefit-risk balance;
- keeping health-care professionals and animal owners informed on changes to authorised veterinary products information.

8.2. Overall Evaluation

Signals of possible unexpected adverse reactions or changes in severity, characteristics or frequency of expected adverse reactions may arise from any source. Rarely, even a single report of an unexpected adverse reaction may contain sufficient information to represent a

signal on or establish a potential causal association with the suspected veterinary products and impact on the benefit-risk balance.

The responsibilities of the MAH, and in particular of the QPPV, are provided in Part I Chapter 2. Requirements for Pharmacovigilance Systems, Monitoring of Compliance and Pharmacovigilance Inspections. 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 veterinary products including appropriate information on post-authorisation safety studies, lack of expected efficacy, information regarding the validity of the withdrawal period or potential environmental problems arising from the use of the veterinary products.

The MAH is obliged to immediately inform the SFDA of any prohibition or restriction imposed by any country in which the veterinary products are marketed and of any other new information which might influence the evaluation of the benefits and risks of the veterinary products concerned. A comprehensive report evaluating the issue and considering the risks in the context of the benefits should be submitted at the earliest opportunity (and no later than the date agreed between the MAH and the SFDA), and should also be discussed in the relevant PSUR.

8.3. Principles of Benefit-Risk Assessment

The benefit-risk assessment of a veterinary products is a complex process based on the intended use and the indications of that product in respect to its overall safety. The assessment should describe and objectively compare the benefits and risks of the veterinary products to evaluate the benefit-risk balance. The reasoning leading to the conclusion should be explained and discussed in a critical manner.

8.4. Optimising the Benefit-Risk Balance

The MAH should aim to optimise the safe use and the benefit-risk balance of an individual veterinary products. Where necessary, the benefit-risk balance may be improved either by increasing the benefits (e.g. including further explanation of how best to use the veterinary products) or by reducing the risks by risk mitigation measures (e.g. by contraindicating the use in animals particularly at risk, reducing dosage, or introducing precautions for use).

When proposing measures to improve the benefit-risk balance of a veterinary products, their feasibility under 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 management actions may be necessary and may be initiated:

- Intensified pharmacovigilance surveillance and post-authorisation safety studies;
- 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 product literature;
- Direct provision of important safety information to veterinarians and other health-care professionals and animal owners (e.g. through letters, bulletins, via electronic media etc.)
- Urgent Safety Restrictions
- Suspension or withdrawal of the marketing authorisation of a veterinary product, in the event that the overall benefit-risk balance is considered unfavourable and proposed risk minimisation measures are considered inadequate. Veterinarians and other health-care professionals and animal owners/the general public should be informed as appropriate. The action previously described should be differentiated from suspension or withdrawal of a veterinary products from the market in the framework of a veterinary products recall for quality/batch-related issues, which may not necessarily affect the MA of the veterinary products in question. Such actions may be taken voluntarily by MAHs.

PART II: Guidelines for Marketing Authorisation Holders On Electronic Exchange of Pharmacovigilance Information

1. INTRODUCTION

Part II of the document focuses on the technical and procedural aspects related to electronic reporting between the different partners. Overall obligations related to expedited reporting and periodic reporting for MAHs please refer to Part I Chapters 5. Adverse Event Reporting and 6. Requirements for Periodic Safety Update Reports.

Electronic reporting obligations shall support the fulfilment of these following main objectives:

- Assist with the rapid and secure transmission of adverse events between partners;
- Fully comply with the respective of international standards;
- Facilitate the electronic reporting by providing the necessary technical tools to the partners;
- Assist the administration and management of adverse events;
- Provide signal detection functionalities and support scientific evaluation of adverse events.

2. ELECTRONIC REPORTING THROUGH COMPANY'S HEADQUARTERS OR VIA A THIRD PARTY

If a pharmaceutical company decides to centralise the electronic reporting (e.g. reporting through the company's headquarters) or to outsource this activity, it remains the MAH's (e.g. the local affiliate) responsibility to ensure that adverse event reports are submitted electronically to 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).
- SFDA should be notified in writing about the arrangement

- Whoever is the physical Sender of the electronic adverse event reports, the MAH (e.g. local affiliate) will remain the contact point for all pharmacovigilance-related matters and responsible for the compliance with the pharmacovigilance obligations.

3. CREATION OF AN ELECTRONIC ADVERSE EVENT REPORT

3.1. General principles on how to create an electronic adverse event report

The reporting to SFDA shall be in an XML message that contains the adverse event information structured and standardised in line with the VICH guideline GL35: pharmacovigilance of veterinary medicinal products: electronic standards for transfer of data (see Annex 2. References).

Overall guidance on the required information for adverse events can be found in Part I Section 5.5. Required information for adverse event reports, including on how to report specific cases e.g. involving adverse events observed in offspring or adverse reactions in animals having been in contact with the treated animals.

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 adverse event report. This applies to all types of reports, i.e. reports with initial information on the case, follow-up information and cases highlighted for nullification.

In follow-up reports, new information should be clearly identifiable in the case narrative section.

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

Where concomitant veterinary 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 may be put in the case narrative.

3.2. Collection of reports

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

For this purpose, a pharmacovigilance system should be developed to allow the acquisition of sufficient information for the scientific evaluation of those reports.

The system should be designed so that it helps to ensure that the collected reports are authentic, legible, accurate, consistent, verifiable and as complete as possible for their clinical assessment.

3.3. Literature reports

The scientific and medical literature is a significant source of information for the monitoring of the safety profile and of the risk-benefit balance of veterinary products, particularly in relation to the detection of new safety signals or emerging safety issues. Marketing authorisation holders are therefore expected to maintain awareness of possible publications through a systematic literature review of widely used reference databases no less frequently than once a week.

The marketing authorisation holder should ensure that the literature review includes the use of reference databases that contain the largest reference of articles in relation to the medicinal product properties. In addition, marketing authorisation holders should have procedures in place to monitor scientific and medical publications in local journals in countries where medicinal products have a marketing authorisation, and to bring them to the attention of the company safety department as appropriate.

KSA specific requirements, as regards medicinal products and scientific and medical publications, which are not monitored by the SFDA and for which valid ISCRs shall be reported by marketing authorisation holders.

3.4. Handling of Languages

Information submitted to SFDA will be coded relevant to the agreed standard terminology (e.g. VeDDRA, species and breeds, country codes etc.). The recommended language for the non-coded information, in particular the narrative section, is English.

3.5. Data privacy laws

To comply with Saudi legislation on the protection of individuals with regard to the processing of personal data, electronic transmission of adverse events should be operated on the principles of anonymised information in accordance with national legislation.

4. TRANSMISSION OF ELECTRONIC REPORTS

4.1 Electronic Transmission of Adverse Events to Be Transmitted On an Expedited Basis

Expedited reporting of adverse events relates to SFDA reporting requirements for adverse events that are to be submitted within 15 days following receipt of the information to SFDA. For detailed requirements, please see Part I section 5.2 Requirements for expedited reporting.

For serious unexpected adverse events reporting from third countries, the information should be sent directly to SFDA.

4.2 Electronic transmission of adverse events not transmitted on an Expedited Basis in Electronic Format

The objective of the periodic transmission of adverse events not previously submitted electronically is to obtain a complete set of adverse events. These data, which are used to facilitate the data review and analysis are submitted complementary to the PSUR.

Where possible, it is strongly recommended that non-expedited adverse events are sent to SFDA.

From a practical point of view, the following principles should be taken into account for the transmission of non-expedited reports in electronic format:

- It is recommended that non-expedited adverse event reports (initial and follow-up) are transmitted at regular intervals by the MAH preferably latest by the time of submission of the PSUR.
- It is recommended that transmissions of non-expedited adverse event reports include all adverse events reportable in a PSUR.
- When third country reports of similar veterinary products need to be submitted, in case when such reports relate to different veterinary products in the Saudi Market with different PSURs, due care should be taken to submit such reports only once to the central database.

From the technical point of view, non-expedited reports should preferably be sent via the same reporting systems as being in use for the submission of expedited reports. Similarly, all available case information for non-expedited reports should be submitted in the same format, as complete as possible. All information for which structured terminology is not available should be added to the narrative section.

4.3 Nullification of Individual Cases

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 “Report identification number” and “Unique case registration number” for previously submitted when identifying a case to be nullified. 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 field “Nullification report” should be set to “Yes” and the nullification reason should be provided in the field “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.
- 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 number for field “Report identification number” and for field “Unique case registration number” should be assigned.
- Individual versions of case reports 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.

Examples of different scenarios for which case nullifications should and should not be carried out:

Scenarios for which individual cases should be nullified:		
#	Example	Action
1	An individual case has been identified as a duplicate of another individual case previously submitted.	<p>One of the individual cases should be nullified. The remaining valid case (considered as the master) should be updated with any additional information that had been reported in the nullified case.</p> <p>It should be considered to include in the narrative of the master that a duplicate case has been nullified with the corresponding information on the sender, the “Report identification number” and “Unique case registration number” of the nullified case..</p>
2	A wrong “Unique case registration number” was accidentally used.	<p>The report with the wrong “Unique case registration number” should be nullified.</p> <p>A new case should be created with a correct “Unique case registration number”.</p>
3	A “Unique case registration number” was accidentally used the same as already been used for a different report and is therefore not unique.	<p>The last entered report should be nullified and re-entered with a new “Unique case registration number”.</p>
4	On receipt of further information it is confirmed that the adverse event occurred before the suspect drug(s) was taken.	<p>The case should be nullified.</p>

5	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 are no longer met.	The case should be nullified.
6	On receipt of further information, it is confirmed that the reported adverse event(s) did not occur to the patient.	The case should be nullified.

Scenarios, for which individual cases should NOT be nullified		
#	Example	Action
1	On receipt of further information on an individual case, it is confirmed that the patient did not receive the sender's (MAH's) suspect drug. However, the patient received other suspect drugs and the minimum reporting criteria for a report are still met.	The case should not be nullified but a follow-up should be sent to update the information.
2	On receipt of further information, the reporter has confirmed that the reported adverse event is no longer considered to be related to the suspect drug(s).	The case should not be nullified. A follow-up report should be submitted with the updated information on the case.
3	Change of the individual case from serious to non-serious (downgrading).	The case should not be nullified. A follow-up report should be submitted with the seriousness flag set to "No".

4.4 Handling of duplicate reports

When a sender has identified a duplicate, it is recommended to nullify one report while ensuring that the remaining report contains all additional information that would be present in the nullified report. The table below gives examples of different scenarios for which nullifications should and should not be carried out. It will also provide information on what to do in specific situations.

ANNEXES

1. GLOSSARY

Term	Abbreviation	Definition
Adverse event		Any observation in animals, whether or not considered to be product-related, that is unfavourable and unintended and that occurs after any use of veterinary products (off-label and on-label uses). Included are events related to a suspected lack of expected efficacy according to approved labelling or noxious reactions in humans after being exposed to veterinary products. Ref. VICH Topic GL24
Adverse reaction		A reaction to a veterinary medicinal product which is harmful and unintended and which occurs at doses normally used in animals for the prophylaxis, diagnosis or treatment of disease or to restore, correct or modify a physiological function.
Animals managed and treated as a group		Animals in intensive food animal production concerning species such as poultry, fish or bees which are managed and treated as a group. In these situations, a certain level of mortality rate is considered as ‘normal’ or ‘expected’. These species are usually treated as a group/flock and only an increase of mortality rate, or severe signs, or animal production losses exceeding the rates normally expected should be considered as serious.
Cascade use		<p>Use of a medicinal product</p> <ul style="list-style-type: none"> - In non-food producing species, and in horses not being intended for slaughter for human consumption, the use of, in the first instance, a veterinary medicinal product which has been authorized for another species or for another condition in the same species at any VICH countries or, if such product is not available, the use of a medicinal product authorised for human use at any VICH countries - In food producing species, providing that the substances included in the products to be used are included in Table I (allowed substances) of the European Regulation 37/2010 and that the veterinarian specifies an appropriate withdrawal period in the first instance, a veterinary medicinal product which has been authorised for another species or for another condition in the same species at any VICH countries or, if such product is not available, the use of a medicinal product authorised for human use at any VICH countries, or a veterinary medicinal product authorised at any VICH countries for in the same or another food-producing species.
Clinical Trials		single scientific experiment conducted in a target species to test at least one hypothesis relevant to the proposed effectiveness claim(s) or to in-use safety in the target animal for a veterinary product under investigation. For the purpose of this guidance, the term clinical study and study are synonymous. This definition originates in the VICH GL9 (GCP) on Good Clinical Practice and is considered synonymous to the term clinical study.
Crisis		An event, which occurs when new information, which could have a serious impact on animal and/or public health, is received for a veterinary medicinal product and which requires immediate action,

Data Lock Point	DLP	A cut-off date for data to be included in a PSUR. It may be set according to the International birth date of the medicinal product. The MAH should in any case submit the PSUR no later than 60 days after the DLP.
Detailed Description of a Pharmacovigilance System	DDPS	Document by which the applicant describes the pharmacovigilance system he/she intends to put in place. It is to be included in the Marketing Authorisation Application
Extensible Markup Language	XML	A subset of SGML that is completely compatible with SGML. (e-term). A data exchange service, which consists of all core standards and functionality required for supporting the standards as currently defined within the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (e.g. Simple Mail Transfer Protocol/Secure Multipurpose Internet Mail Extension - SMTP/SMIME- protocol). (e-term)
Gulf Cooperation Countries	GCC	(Saudi Arabia, United Arab Emirates, Kingdom of Bahrain, Kuwait, Oman, State of Qatar)
International Birth Date	IBD	The date of the first marketing authorization for a same or similar product granted anywhere in the VICH region.
International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products	VICH	trilateral (EU-Japan-USA) programme aimed at harmonizing technical requirements for veterinary product registration
Lack of expected efficacy		The apparent inability of an authorised product to have the expected efficacy in an animal, according to the claims of the SPC and following use of the product in accordance with the SPC. In the following text this guideline will not include the word 'suspected' when making full text reference to lack of expected efficacy.
Marketing Authorisation Holder	MAH	A person or entity who/which holds the authorisation of a veterinary product.
Off-label use		The use of a veterinary medicinal product that is not in accordance with the SPC, including the misuse and serious abuse of the product.
Postauthorisation safety studies		Pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying and investigating a safety hazard relating to an authorised veterinary medicinal product.
Periodic Safety Update Report	PSUR	A periodical scientific report on adverse events and other issues within the scope of pharmacovigilance that have been reported to a MAH during a specific period.

PSUR, abridged		A PSUR that contains less information than a full PSUR and that contains only administrative data, and which has been prepared for a non-marketed product for which no reports have been received during the period
Serious adverse event		An adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect. For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event. See VICH Topic GL 24.
Serious adverse reaction		An adverse reaction which results in death, is life-threatening, results in significant disability or incapacity, is a congenital anomaly/birth defect, or which results in permanent or prolonged signs in the animals treated. Life-threatening in this context refers to a reaction in which the animal was at risk of death at the time of the reaction.
Summary of Product Characteristics	SPC	A document that contains the information on the condition of use of a veterinary medicinal product as developed during the course of the assessment process.
Unexpected adverse event		An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labelling or approved documents describing expected adverse events for a veterinary product. Ref. VICH Topic GL 24
Urgent safety restrictions		An interim change to the product information due to new information having a bearing on the safe use of the medicinal product, concerning particularly one or more of the following items in the SPC: therapeutic indications, posology, contraindications, warnings, target species, and withdrawal periods.
Veterinary Dictionary for Drug Regulatory Activities	VeDDRA	A list of standard clinical terms to be used in reporting suspected adverse reactions in animals or humans after exposure to veterinary medicinal products
Veterinary Products		Any substance or combination of substances presented as having properties for treating or preventing disease in animals; or which may be used in or administered to animals 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. (Article 1 of the GCC veterinary products Directive)

2. REFERENCES:

1. CVMP List on Additional Controlled Terminology for electronic submission of Reports on Adverse Reactions to Veterinary Medicinal Products (EMEA/556/04, latest version).
2. European Commission (2011). Volume 9B - Pharmacovigilance for Medicinal Products for Veterinary Use Guidelines on Pharmacovigilance for Medicinal Products for Veterinary. Accessed in Aug, 2019, available at: https://ec.europa.eu/health/documents/eudralex/vol-9_en
3. GCC Veterinary Products Directive and its Executive Regulation, Available at:
https://www.sFDA.gov.sa/ar/drug/drug_reg/DocLib/20%النظام%20%المستحضرات%20%البيطري/ and
https://www.sFDA.gov.sa/ar/drug/drug_reg/DocLib/20%النظام%20%اللائحة%20%التنفيذية%20%للقانون%20%البيطري/
https://www.sFDA.gov.sa/ar/drug/drug_reg/DocLib/20%النظام%20%المستحضرات%20%البيطري%20%التعاون%20%الدول%20%الخليج%20%العربية/
4. List of Species and Breeds for Electronic Reporting of Suspected Adverse Reactions in Veterinary Pharmacovigilance (EMEA/CVMP/553/03, latest version).
5. The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) (<http://www.vichsec.org/>):
 - VICH Topic GL9 Guidelines On Good Clinical Practice.
 - VICH Topic GL 24 on Pharmacovigilance of Veterinary Medicinal Products: Management of Adverse Event Reports (AERs).
 - VICH Topic GL 29 on Pharmacovigilance of Veterinary Medicinal Products: Management of Periodic Summary Update Reports (PSURs).
 - VICH Topic GL30 Guideline on Pharmacovigilance of Veterinary Medicinal Products Controlled Lists of Terms.
 - VICH GL35 Pharmacovigilance of Veterinary Medicinal Product: Electronic Standards for Transfer of Data.
 - VICH Topic GL42 Guidelines on Pharmacovigilance of Veterinary Medicinal Products - Data Elements for Submission of Adverse Event Reports.
6. VeDDRA List of Clinical Terms for Reporting Suspected Adverse Reactions in Animals and Humans to Veterinary Medicinal Products (EMA/CVMP/10418/2009, latest version).