Central Administration Pharmaceutical Care
General Administration For Pharmceutical Vigilance

Draft Guideline for Veterinary medicine good pharmacovigilance practices in Egypt (VGVP) 2025

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Contents

Introduction:

Pharmacovigilance in Egypt has gained increasing importance in recent years as part of the country`s efforts to strengthen the regulation and safety monitoring of all medicinal products.

It refers to the science and activities related to the detection, assessment, understanding and prevention of adverse events or any other problems associated with medicinal products.

Veterinary pharmacovigilance involves closely monitoring the safety and efficacy of veterinary medicines on the Egyptian market. The pharmacovigilance general administration (PVGA) has a coordinating role in the Egyptian pharmacovigilance system and operates services and processes to support veterinary pharmacovigilance activities. PVGA also provides guidance and recommendations to stakeholders on the safe and effective use of veterinary medicines.

Veterinary good pharmacovigilance practices (VGVP) are a set of measures to facilitate pharmacovigilance for veterinary medicines in Egypt.

Scope:

This guidelines for pharmacovigilance of veterinary medicines in Egypt define the framework and procedures necessary to ensure the continuous monitoring of safety, quality and efficacy of veterinary medicinal products throughout their lifecycle.

Abbreviations:

ACO	Addendum of clinical overview
AE	Adverse event
AR	Adverse reaction
DLP	Data Lock Point
EDA	Egyptian drug authority
ESI	Emerging safety issue
ICSR	Individual Case Safety Report
LSR	Local Safety Responsible
MAH	Marketing authorization holder
PASS	Post-authorization safety studies
PL	Package leaflet
PSMF	Pharmacovigilance system master file
PSSF	Pharmacovigilance sub-system file (on national level)
PVGA	Pharmacovigilance general administration
QPPV	Qualified person responsible for pharmacovigilance
SmPC	Summary of product characteristics
SOC	System organ class (in VEDDRA)
VEDDRA	Veterinary Dictionary for Drug Regulatory Activities
VGVP	Veterinary good pharmacovigilance practices
WHO	World Health Organization

Definitions:

Glossary:

- Benefit risk evaluation report/Addendum of clinical overview (ACO)

A critical document addressing the current benefit/risk balance for the product on the basis of a consolidated version of safety/efficacy data accumulated since the initial MAA or the last renewal, taking into account suspected adverse reactions reports, additional pharmacovigilance activities and the pharmacovigilance activities contained in the risk management document, if applicable

- Adverse event (AE)

Any observation in animals whether or not considered to be product related, that is unfavorable 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 labeling or noxious reactions in humans after being exposed to veterinary products.

- Adverse reaction (AR)

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.

- Animal healthcare professional

Terminology used in the context of good veterinary pharmacovigilance practice (VGVP) guidance when referring to healthcare professionals working with animals including, for example, veterinarians, para-veterinarians (i.e. veterinary nurse, veterinary technician and veterinary assistants) etc

- Data Lock Point:

A cut-off date for data to be included in Benefit risk evaluation report/Addendum of clinical overview. It may be set according to the International birth date of the medicinal product. The MAH should in any case submit the Benefit risk evaluation report/Addendum of clinical overview no later than 60 days after the DLP.

- Emerging safety issue

A safety issue considered to require urgent attention because of the potential major impact on the benefit-risk balance of the concerned veterinary medicinal product, on animal or public health, or protection of the environment, to the point that urgent regulatory action and communication may

be needed.

- Environmental incident

A situation where an ecosystem is adversely affected through exposure to a veterinary medicinal product, its active substance(s) or its metabolites present in different environmental compartments (e.g. soil, water) or animal remains. Such incidents may consist of, for example, presence of the active substances in soil or water or wildlife poisoning by a substance to levels considered harmful for the ecosystem affected. Events related to user safety are not considered environmental incidents.

- Individual Case Safety Report (ICSR)

It is the format and content for the reporting of one or several suspected adverse reactions in relation to a veterinary product that occur in a single animal at a specific point of time.

- Medically important VeDDRA term

A list of selected relevant VeDDRA terms per species used for prioritization of signal management.

- Pharmacovigilance alert

Potential concerns, including emerging safety issues arising from pharmacovigilance data or other information impacting animal or public health or the environment that may require urgent consideration by the competent authority responsible for the veterinary medicinal product(s).

- Pharmacovigilance system

A system used by the marketing authorization holder and by EDA to fulfill the pharmacovigilance tasks and responsibilities listed in national regulations and designed to monitor the safety of authorized veterinary products and detect any change to their risk-benefit balance. In general, a pharmacovigilance system is a system used by an organization to fulfill its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance.

- Pharmacovigilance system master file (PSMF)

A detailed description of the pharmacovigilance system used by the marketing authorization holder with respect to one or more authorized veterinary products. See also Pharmacovigilance system.

- Post-authorization safety studies

Pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the

marketing authorization, conducted with the aim of identifying and investigating a safety hazard relating to an authorized veterinary medicinal product.

- Post-marketing surveillance study

Any study with an authorized veterinary medicinal product under normal condition of marketing, which is conducted to identify, describe or quantify a safety risk, including a lack of efficacy, to confirm the safety profile (including environmental safety) and efficacy of a veterinary medicinal product or to measure the effectiveness of risk management measures.

- 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.

- Serious adverse event

An adverse event which results in death, 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

- Signal

Information arising from one or multiple sources, including observations and experiments, which suggests a new potentially causal association, or a new aspect of a known association between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action.

- Signal detection

The process of looking for and/or identifying signals using data from any source.

- Suspected adverse event reporting

  It is the primary information source for post-authorization safety monitoring for medicinal products, including veterinary medicinal products, and provides most of the data for the evaluation of the benefit-risk profile of a medicinal product.

- Unexpected adverse event

An unexpected adverse event is an adverse event of which the nature, severity or outcome is not consistent with approved labeling or approved documents describing expected adverse events for

a veterinary product.

- 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

- 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 good pharmacovigilance practices (VGVP)

Veterinary good pharmacovigilance practices (VGVP) are a set of measures to facilitate pharmacovigilance for veterinary medicines in Egypt.

1- Pharmacovigilance systems and their quality management System & pharmacovigilance master file:

1.1- Introduction:

This module of the guidelines on veterinary good pharmacovigilance practices (VGVP) addresses the basic requirements on the pharmacovigilance system, its integral quality management system and the pharmacovigilance system master file (PSMF) that marketing authorization holders for veterinary medicinal products authorized in Egypt should establish and maintain.

1.2- Pharmacovigilance system master file (PSMF):

According to EDA chairman degree 625/2024, marketing authorization holders shall establish and maintain a system for collecting, collating and evaluating information on the suspected adverse events concerning their authorized veterinary medicinal products ('pharmacovigilance system'), enabling them to fulfill all their pharmacovigilance obligations.

The overall objectives of a pharmacovigilance system are:

- promoting the safe and effective use of veterinary medicinal products, in particular through providing timely information about the safety of veterinary medicinal products and their impact to public health, animal health, animal welfare and the environment;
- detecting and taking measures to prevent harm to animals and humans from adverse events and harm to the environment arising from the use of or exposure to authorized veterinary medicinal products within or outside the terms of the marketing authorizations; and
- Complying with the legal requirements for pharmacovigilance tasks and responsibilities.

The pharmacovigilance system of the marketing authorization holder shall be fully functional and described clearly and unambiguously in the pharmacovigilance system master file. The marketing authorization holder may, where appropriate, use separate pharmacovigilance systems for different categories of veterinary medicinal products. For example, a single marketing authorization holder may establish more than one pharmacovigilance systems specific for particular types of veterinary medicinal products (vaccines, pharmaceuticals, etc.). Each such system shall be described in a separate pharmacovigilance system master file. For each veterinary medicinal product, the marketing authorization holder shall not have more than one pharmacovigilance system described in a pharmacovigilance system master file.

The marketing authorization holder shall be responsible for the pharmacovigilance of the

veterinary medicinal product(s) for which it holds a marketing authorization and shall continuously evaluate by appropriate means the benefit-risk balance of their veterinary medicinal product(s) and, if necessary, take appropriate measures to minimize the risk. The marketing authorization holder's risk management system consists of all procedures and processes for monitoring the benefit-risk balance of veterinary medicinal products and performing signal management and includes communication. Marketing authorization holders shall ensure continuous assessment and document the risk management measures and the outcome of risk minimization measures in the pharmacovigilance system master file for the veterinary medicinal products for which specific safety monitoring requirements exist.

Where the pharmacovigilance tasks have been contracted/subcontracted out by the marketing authorization holder to a third party, those arrangements shall be set out in detail in the pharmacovigilance system master file. The marketing authorization holder shall retain full responsibility for all pharmacovigilance obligations contracted/subcontracted to third and therefore the arrangements with third parties should cover how oversight and compliance with legal requirements can be ensured. Contracted/subcontracted person(s) or any other third party carrying out pharmacovigilance activities in whole or in part, on behalf of or in conjunction with marketing authorization holders, shall accept to be audited by or on behalf of marketing authorization holders.

The marketing authorization holder shall comply with good pharmacovigilance practice for veterinary medicinal products. In addition to this Module, for key pharmacovigilance processes dedicated Modules are included in veterinary good pharmacovigilance practice guidance, as follows:

- Module on Collection and recording of suspected adverse events for veterinary medicinal products.
- Module on Signal management.
- Module on Benefit risk evaluation report/Addendum of clinical overview.
- Module on safety description document

1.3- Qualified person responsible for pharmacovigilance (QPPV)

The QPPV designated by the marketing authorization holder should have oversight of the pharmacovigilance system in terms of structure and performance and be in a position to ensure the fulfillment of the tasks either directly or through delegation and supervision. The oversight referred to above should cover the functioning of the marketing authorization holder's pharmacovigilance system in all relevant aspects, including:

- Quality control and assurance procedures;
- Standard operating procedures;
- PSMF preparation and maintenance;

- Database operations;
- Safety reporting;
- Signal management;
- Post-marketing surveillance studies;
- Communication to stakeholders;
- Contractual/sub contractual arrangements, compliance data (e.g. in relation to the quality, completeness and timelines for safety reporting and signal management), audit reports;
- Preventive or corrective action plan preparation and implementation; and
- Training of personnel in relation to pharmacovigilance.

It is recognized 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 medicinal products covered by the marketing authorization holder's pharmacovigilance system. The QPPV may therefore delegate specific tasks, with appropriate oversight, to appropriately qualified and trained individuals, e.g. acting as experts on the safety aspects of certain veterinary medicinal products, provided that the QPPV maintains system oversight and overview of the safety profiles of all veterinary medicinal products. Such delegation should be documented in the PSMF.

The marketing authorization holder shall ensure that:

- QPPV has acquired adequate theoretical and practical knowledge for the performance of pharmacovigilance activities.
- QPPVs shall have a minimum of bachelor degree of Veterinary Medicine, pharmacy or Human medicine (with veterinary experience).

The hierarchical relationship of the QPPV shall be defined in an organizational chart together with those of other managerial and supervisory staff. In case the tasks of the QPPV are outsourced to a third party those arrangements shall be specified in detail in the contract and included in the PSMF.

Usually, the QPPV will be designated to a single pharmacovigilance system and respective PSMF. It is acceptable for the same QPPV to provide services for more than one marketing authorization holder, for a shared or for separate pharmacovigilance systems. The marketing authorization holder may subcontract certain activities of the pharmacovigilance system to third parties, i.e. to a PV service provider organization "not individuals, the freelance person is not applicable in Egypt.

Back-up arrangements that apply in the absence of the QPPV should be in place and described in the PSMF.

The marketing authorization holder shall ensure that the QPPV has sufficient authority to influence the performance of the quality management system with regard to pharmacovigilance and the pharmacovigilance activities of the marketing authorization holder. The marketing authorization holder should therefore ensure that the QPPV has authority over and access to the PSMF and approves/authorizes any changes to it. The authority over the pharmacovigilance system and the PSMF allows the QPPV to implement changes to the system as well as to initiate regulatory action in response to emerging safety concerns.

When a marketing authorization holder intends to expand its veterinary medicinal product portfolio, for example by acquisition of another company or by purchasing individual marketing authorizations from another marketing authorization holder, the QPPV should be notified well before the transfer of pharmacovigilance activities in order to ensure that the potential impact on the pharmacovigilance system can be assessed and the system can be adapted accordingly. The QPPV should be involved in determining what pharmacovigilance data is to be requested from the other marketing authorization holder, either pre- or post-acquisition. In this situation, the QPPV should review the sections of the contractual arrangements that relate to responsibilities for pharmacovigilance activities and safety data exchange (either as part of a general template or on a case by case) and have the authority to request amendments.

When a marketing authorization holder intends to establish a partnership with another marketing authorization holder, organization or person that has a direct or indirect impact on the pharmacovigilance system, the QPPV should be informed in sufficient time to allow for required changes to the pharmacovigilance system to be made and be involved in the preparation of the corresponding contractual arrangements so that all necessary provisions relevant to the pharmacovigilance system are included to enable the QPPV to fulfil the responsibilities.

1.4- Quality system management:

Marketing authorization holders shall establish and use quality management systems that are adequate and effective for the performance of their pharmacovigilance activities.

Quality management system means a formalized system that provides for comprehensive processes, procedures, and responsibilities for achieving quality policies and objectives to coordinate and direct an organization's activities and improve its effectiveness and efficiency in this regard on a continuous basis.

While there has to be compliance with these legal requirements, the implementation of a quality system should be adapted to the respective organization. The application of the quality system should be adapted to how crucial each pharmacovigilance task is for fulfilling the objectives for each veterinary medicinal product covered by a pharmacovigilance system. The quality system

shall be based on all the following activities:

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

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

- Reviews of the systems by those responsible for management;
- Audits;
- Compliance monitoring;
- Inspections;
- Evaluating the effectiveness of actions taken with veterinary medicinal products for the purpose of minimizing risks and supporting their safe and effective use.

The quality management system shall be described in the pharmacovigilance system master file Relevant documents include:

- Documents on assignment of roles, responsibilities and authorities to all personnel directly involved in pharmacovigilance tasks;
- Job descriptions defining the duties of the managerial and supervisory staff;
- Training plans and records;
- Instructions for the compliance management processes;
- Appropriate instructions on the processes to be used in case of urgency, including business continuity;
- Performance indicators where they are used to continuously monitor the good performance of pharmacovigilance activities;
- Reports of audits and follow-up audits, including their dates and results;
- Methods of monitoring the efficient operation of the quality system and, in particular, its ability to fulfil the quality objectives;
- Records to demonstrate that deficiencies and deviations from the established quality system are monitored, that corrective and preventive actions have been taken, that solutions have been applied to deviations or deficiencies and that the effectiveness of the actions taken has been verified.

1.4.1. Written procedures:

An essential element of any pharmacovigilance system is that there are clear written procedures in place. The quality management system shall include detailed policies, processes and procedures, documented in the PSMF, for at least, but not necessarily limited to, pharmacovigilance:

1. Initial recording of suspected adverse event.
2. Collection of additional data.
3. Collation of reports of suspected adverse events and additional data.
4. Data handling other than mentioned in points (1) to (3) of this list.
5. Evaluation of data.
6. Monitoring the quality, integrity and completeness of all information registered in the pharmacovigilance system including, but not restricted to, the information reported to the EDA and management of duplicates.
7. Recording of adverse event in the pharmacovigilance database.
8. Archiving of all relevant documents.
9. Risk management system including processes for:
    - Signal management.
    - Continuous monitoring of the benefit-risk balance of veterinary medicinal products .
    - Overarching communication plan.
10. Document management system.
11. Training.
12. Audit.

In each area, the marketing authorization holder should be able to provide evidence of a system that supports appropriate and timely decision making and action. The list of written procedures should also be available and should comprise the procedural document reference number, title, effective date and document type (for all standard operating procedures, work instructions, manuals etc.) and details on how the procedures can be accessed. Procedures belonging to service providers and other third parties should be clearly identified. Documents relating to specific local/country procedures need not be listed, but a list may be requested on a per country basis.

1.4.2. Performance indicators:

The organization shall use relevant performance indicators to continuously monitor the performance of pharmacovigilance activities in relation to the quality requirements. The items of information that can be collected at regular intervals to track the performance of the system should be realistic and measurable, such as submission timeliness or quality of reports / reports

free of errors. A list of these performance indicators including the reason why they have been chosen, if applicable, and a description on how to use them should be included in Section E (5) reflected in Annex 4 of the PSMF.

1.4.3. Audits:

Marketing authorization holders shall perform audits of the pharmacovigilance system at regular risk- based intervals to ensure that it complies and to determine the pharmacovigilance system effectiveness. Audits of the pharmacovigilance system should ensure that it complies with the legal requirements, the human resource management, the compliance management, the record management and data retention and to ensure its effectiveness. A report shall be drawn up on the results for each audit and any follow-up audits and these shall be sent to the QPPV and management responsible for the matters audited, as applicable, to ensure that management cooperates with the QPPV to address the findings. The report should include the results of audits of organizations or persons the marketing authorization holder has delegated tasks to, as these are part of the marketing authorization holder‘s pharmacovigilance system. The risk-based audit schedule and the report on each audit and follow-up audit, including their dates and results shall be documented in Section E and Annex 4 of the PSMF, as applicable. The process for risk-based planning shall be described and the rationale documented in the PSMF. Contracted/subcontracted person(s) or any other third party carrying out pharmacovigilance activities in whole or in part, on behalf of or in conjunction with marketing authorization holders, shall accept to be audited by or on behalf of marketing authorization holders.

1.4.4. Corrective and preventive action plan:

The marketing authorization holder’s corrective and preventive action plan shall document in writing a robust, effective and useful process systematically addressing and minimizing identified risk or defects. It shall be clear and precise and address timelines for action. Marketing authorization holders shall monitor the implementation and assess the effectiveness of corrective and preventive actions. If there are changes associated with the corrective and preventive actions, those changes shall be evaluated and be part of a controlled process of change (change management) and communicated to relevant stakeholders.

In particular as a consequence of audits, corrective action(s), including a follow-up audit on deficiencies identified, shall be taken where necessary. Additionally, corrective and preventive actions should be drawn for non-compliance identified during inspections by the competent authorities aiming at monitoring the compliance of marketing authorization holders with legally required pharmacovigilance tasks and responsibilities. Associated corrective and preventive actions shall be documented for the last 5 years.

1.4.5. Training of personnel for pharmacovigilance:

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

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

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

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

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

Adequate training should also be considered by the organization for those staff members to whom no specific pharmacovigilance tasks and responsibilities have been assigned but whose activities may have an impact on the pharmacovigilance system or the conduct of pharmacovigilance. Such activities include but are not limited to those related to clinical trials, technical product complaints, medical information, sales and marketing, regulatory affairs, legal affairs and audits.

Appropriate instructions on the processes to be used in case of pharmacovigilance-related urgency, including business continuity, shall be provided by the organization to their personnel.

1.4.6. Document management system:

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

A document management system shall be put in place for all documents related to pharmacovigilance activities, ensuring their retrievability as well as traceability of the measures

taken to investigate safety concerns, of the timelines for those investigations and of decisions on safety concerns, including their date and the decision-making process. The document management system shall include a record management system for receiving, recording, collecting and assessing information on adverse events.

All information technology (IT) systems, (electronic) storage spaces and record management systems including database systems used as part of pharmacovigilance activities should be located, designed, constructed, adapted and maintained to suit their intended purpose in line with the quality objectives for pharmacovigilance. These systems should be subject to appropriate checks, qualification and/or validation activities to prove their suitability for the intended purpose. Evidence on validation status of the system(s) used should be available upon request, if applicable. There should be appropriate structures and processes in place to ensure that pharmacovigilance data and records are protected from destruction during the applicable record retention period.

As part of a record management system, specific measures should be taken at each stage in the storage and processing of pharmacovigilance data to ensure data security, integrity and confidentiality. This should involve strict limitation of access to records and to databases to authorized personnel respecting the confidentiality of the data. For systems critical for the conduct of pharmacovigilance it should be ensured to build into the system the creation of a record of all pharmacovigilance data changes and deletions (a system generated "audit trail"). For change or deletion of pharmacovigilance data the reason should be documented. Audit trails need to be available.

1.4.7. Quality management system requirements for pharmacovigilance tasks contracted/subcontracted by the marketing authorization holder:

Where a marketing authorization holder has contracted/subcontracted part or all of its pharmacovigilance tasks, it shall retain full responsibility for ensuring that an effective quality management system is applied in relation to those tasks. All legislative and guidance requirements are also applicable to the other organization (third party) to which the tasks have been contracted/subcontracted even if it is located outside Egypt.

When contracting/subcontracting tasks to a third party, the marketing authorization holder shall include contract(s) with the third party and these should be detailed, up-to-date and clearly document the allocation of tasks and responsibilities between the marketing authorization holder and the third party. A description of the contracted/subcontracted activities and/or services and a list of the contracts with contractors/subcontractors, specifying the veterinary medicinal product(s) and territory (-ies) concerned, shall be included in the PSMF. The third party may be

subject to inspection by PVGA according to the tasks and responsibilities delegated to them.

Contractual arrangements should be prepared with the aim of enabling compliance with the legal requirements by each party involved. The third party may not subcontract any task assigned to it by the marketing authorization holder without the marketing authorization holder's written consent. When preparing contractual arrangements, the marketing authorization holder should include sufficiently detailed descriptions of the delegated tasks, the related interactions and data reconciliation, together with, for example, agreed definitions, tools, assignments and timelines. The contractual arrangements should also contain clear information on the practical conduct of the outsourced tasks, including those for the maintenance of pharmacovigilance databases, if applicable. Further, they should indicate which processes are in place for verifying whether the agreed arrangements are being adhered to on an ongoing basis. In this respect, e.g. regular risk-based audits of the third party by the marketing authorization holder are required.

1.5- Pharmacovigilance system master file (PSMF):

1.5.1. Summary of the pharmacovigilance system master file:

Summary of the applicant's pharmacovigilance system Except in the situations described in the accessibility of PSMF/PSSF, where the full PSMF/PSSF (along together with its summary) is requested to be submitted only a summary with any nomination and denomination of PV staff, which shall include in addition the following elements :

- The contact details and full data and information (national ID, official nomination letter, certificates, any change in PV staff ...etc.) which are required for the qualified person and all PV staff .
- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance;
- The full contact details of the qualified person;
- A statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the pharmacovigilance tasks and responsibilities listed in this GVP chapters ;
- A reference to the location where the pharmacovigilance system master file for the veterinary medicinal product is kept .

Marketing authorization holders shall ensure that the entries in the product database for veterinary medicinal products are always up-to-date, including the information about the QPPV, name and contact details (telephone numbers for continuous availability, email address, postal address and operational location of the QPPV) and PSMF version number and location information.

Each PSMF can be declared only in one location in the applicant's summary of

pharmacovigilance system master file and subsequently in the product database and this single location should be registered as part of controlled organization data. The address of the location of the PSMF provided should be a physical office address which reflects either the site in Egypt where the main pharmacovigilance activities of the marketing authorization holder are performed or the site where the QPPV operates. This address may be different to that of the applicant/marketing authorization holder, for example it may be a different office of the marketing authorization holder or the address of a third party undertaking the main activities. Where the PSMF is held in electronic form, the location stated must be a site where the data stored can be directly accessed, and this is sufficient in terms of a practical electronic location. When determining the main site of pharmacovigilance activity, the marketing authorization holder should have an appropriate rationale for the location decision. In the situation where the main activities take place outside Egypt, or where a main site cannot be determined, the location should default to the site where the QPPV operates.

1.5.2. Pharmacovigilance system master file content:

The PSMF is a legal requirement in Egypt and is applicable for any veterinary medicinal product authorized in Egypt, irrespective of the marketing authorization procedure. Apply Irrespective of the location of other activities, the QPPV's residence, the location at which he/she carries out his/her tasks and the PSMF location must be within Egypt. The content of the pharmacovigilance system master file should reflect availability of local safety information for veterinary medicinal products authorized in Egypt, presenting information on the pharmacovigilance system applied at national level. The content shall be indexed to allow for efficient navigation in the document and follow the structure described, on the format and content of the pharmacovigilance system master file. The PSMF shall describe the pharmacovigilance system in place at the current time.

The PSMF shall consist of a main part and Annexes containing the information, and as shown in Table 1. The sections in the main part of the PSMF should contain information that is fundamental for the description of pharmacovigilance system whereas the corresponding Annexes should include supplementary information for each section that may change frequently.

Table 1: Content of the PSMF:

PSMF section	Main part	Annexes
Information on the PSMF	Section A	Annex 1 (logbook)
QPPV, Assisting veterinary surgeon, and back up procedures	Section B	Annex 2
Marketing Authorization holder information	Section C	Annex 3
Document management system (including record management system for adverse event recording)	Section D	
Quality management system for pharmacovigilance activities	Section E	Annex 4
Contractual arrangements between marketing authorization holders and third parties concerning pharmacovigilance activities	Section F	Annex 5
Products	-	Annex 6

- ✓ Section A Information on the PSMF, Annex 1(Logbook)

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

- ✓ Section B QPPV, Assisting veterinary surgeon, and back up procedures, Annex 2
  - All documents for qualification and experience evidences. (Required for all PV staff).
  - The list of tasks that have been delegated by the QPPV/LSR, or the applicable procedural document
  - The curriculum vitae of the QPPV/LSR and associated documents
  - Contact details
- ✓ Section C Marketing Authorization holder information, Annex 3
  - A description of the organizational structure of the marketing authorization holder relevant to the pharmacovigilance system shall be provided. The description shall provide a clear overview of the company (ies) involved, the main pharmacovigilance departments and the relationship(s) between organizations and operational units relevant to the fulfillment of pharmacovigilance obligations
  - Official organogram(s)
- ✓ Section D Document management system (including record management system for adverse event recording)
  - Lists associated with the description of sources of safety data e.g. affiliates and third-party Contacts.
  - Flow diagrams to indicate the main stages, timeframes and parties involved in

safety data collection and its outcome.

- ✓ Section E Quality management system for pharmacovigilance activities and Annex 4:
  - KPIs
  - Audit schedules
  - List of audits conducted and completed
- ✓ Section F Contractual arrangements between marketing authorization holders and third parties concerning pharmacovigilance activities and Annex 5:
  - The lists of contracts and agreements
  - A copy of the individual contractual agreements relevant to Egypt.
- ✓ Products, Annex 6
  - List(s) of products covered by the PSMF
  - Any notes concerning the MAH per product

1.5.3. Pharmacovigilance system master file location, availability and maintenance:

The pharmacovigilance system master file shall be located either at the site where the main pharmacovigilance activities are performed or at the site where the qualified person responsible for pharmacovigilance operates, irrespective of the format (paper-based or electronic format file). Based on this rule, the PSMF shall be located in Egypt, an exception is in the situation where the main activities take place outside Egypt (e.g. multinational MAHs/applicants), the location shall default to the site where the QPPV operates or where the main pharmacovigilance activities are performed (e.g. located in the country of headquarter) provided that:

- ✓ The PSMF is made available to EDA at any time; and
- ✓ The local office/ affiliate of the MAH/applicant has detailed description on the pharmacovigilance system/ activities on the local level. Details about the location of the pharmacovigilance system master file are required to be notified to EDA, and any change to the location shall be notified immediately to EDA in order to have the information updated. The required location information for the PSMF is a physical office address of the marketing authorization holder or a contracted third party. Where the pharmacovigilance system master file is held in electronic form, the location stated shall be a site where the data stored can be directly accessed, and this is sufficient in terms of a practical electronic location. When determining the main site of pharmacovigilance activity, the marketing authorization holder shall consider the most relevant site for the pharmacovigilance system as a whole, since the relative importance of particular activities may vary according to products and fluctuate in the short term. The marketing authorization holder shall have an appropriate rationale for the location decision. In the situation where a main site cannot be determined, the location shall default to the site where the QPPV operates.

2-Signal Management

2.1 Introduction

This module provides general principles and guidance on the scientific and quality aspects of the signal management process for veterinary medicinal products. In addition, it describes roles, responsibilities, and procedural aspects in the setting of the signal management practices overseen by the Pharmaceutical Vigilance General Administration – PVGA.

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

2.2 Structures and processes:

2.2.1 Signal management activities by marketing authorization holders

Marketing authorization holders should continuously monitor the safety of their veterinary medicinal products, in order to promptly detect any new safety issues that may impact the benefit-risk balance so that adequate regulatory actions and communication (where necessary) can be taken in coordination with the competent authorities and the Agency. New safety issues may include a new risk associated with the product or the active substance or a change to a known risk.

A signal is defined as information that arises from one or multiple sources, including observations and experiments, which suggests a potentially new causal association, or a new aspect of a known causal association between an intervention and an adverse event or a set of related adverse events, that is judged likely to justify further investigation of possible causality.

New aspects of a known association may include changes in the frequency, distribution (e.g. gender, age, breed, and country), duration, severity, or outcome of an adverse reaction.

A signal often relates to all veterinary medicinal products containing the same active substance, including combination products. Certain signals may only be relevant for a particular veterinary medicinal product or in a specific indication, strength, pharmaceutical form, or route of administration, whereas some signals may apply to a whole class of veterinary medicinal products.

The identification of new risks associated with a veterinary medicinal product should be based on the detection and analysis of signals, in accordance with the signal management process. The signal management process should consist of, but not be limited to, the pharmacovigilance activities of **signal detection, prioritization, validation, assessment, and recommendation for action.**

In case of an impact on the benefit-risk balance of the veterinary medicinal product

concerned, on animal health and welfare or public health, or on protection of the environment that is considered an emerging safety issue, the marketing authorization holder should notify it to PVGA without delay and no later than 5 working days following their identification (see section 2.2.4.b named emerging safety issue).
Where the outcome of the signal management process identifies a change to the benefit-risk balance or a new risk, the marketing authorization holder shall notify it without delay and no later than 45 calendar days to PVGA.

2.2.2 Data sources in signal management

Signals can arise from several data sources, including all scientific information from the use of veterinary medicinal products, i.e. quality, non-clinical, clinical data, and post-marketing data.

The most common sources for detecting signals include spontaneous reporting systems, clinical studies, and scientific literature. Marketing authorization holders shall carry out signal management for their veterinary medicinal products, taking into account all relevant pharmacovigilance data of which they can reasonably be expected to be aware and which may be useful for that signal management process, including sales data.

2.2.3 Signal detection

Depending on the size and nature of the database used, signal detection may involve the review of individual spontaneous reports, the use of statistical analyses, or a combination of both. Aggregated data analyses and the use of several data sources can also increase the quality of the process.

2.2.4 Signal prioritization

Signal management should follow a risk-based approach that takes into account the type of veterinary medicinal product or active substance concerned, the length of time on the market, and the stability of the pharmacovigilance profile (i.e., based on knowledge gained about the safety and efficacy of the product over its full life cycle).

In order to avoid delaying the detection and management of certain signals that might require urgent attention, signal prioritization should be performed throughout the whole signal management process, from signal detection to signal assessment. Prioritization furthermore allows for identifying and focusing on those signals with a potential for significant impact on the benefit-risk balance of the veterinary medicinal product or its active substance, or those signals with a high impact on animal or public health and thus require more urgent attention.

Appropriate measures should be considered at any stage if the information available suggests that there could be a risk that requires prevention or risk minimization in a timely manner. Clinical judgment and flexibility should be applied throughout the process.

a) The following criteria can be considered for signal prioritization

- Novelty of the veterinary medicinal product-event association. The focus should be on new associations or new aspects of a known association, such as a change in frequency, severity, duration or temporal persistence, further anatomical specification, change in the outcome or reported fatality rate.
- Strength of the evidence supporting the association, including the number of case reports.
- Seriousness, severity, outcome or reversibility of the event involved and the potential for prevention.
- Statistical disproportionality measure value (not exclusive, i.e. a non-significant value does not exclude a potential signal).
- Public health and environmental protection implications.
- Species-specific events.

Results from previous analyses of identified signals can be used as a prioritization criterion, e.g. a signal that was previously refuted, but where new cases are expected to provide further supporting evidence and re-opening of the signal.

In some cases, signals that could cause media attention and/or public concerns may deserve special attention. These include situations where compliance with certain treatments or public health measures may be affected by misinformation originating in e.g. the general public at risk of not adhering to proven vaccination schemes in pets on the basis of unfounded information in social media.

b) Emerging safety issues:

Any new information which might influence the assessment of the benefits and the risks of veterinary medicinal product should be identified as an emerging safety issue. It should be reported to the PVGA, without delay and no later than 5 working days after publishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue and

Examples include:

- Major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpected increase in rate of fatal or life-threatening adverse events;
- Major safety issues identified through spontaneous reporting or published in the scientific literature, which may lead to considering a contraindication, a restriction of use of the veterinary medicinal product or its withdrawal from the market;
- Major safety-related regulatory actions outside Egypt, e.g. a restriction of the use of the veterinary medicinal product or its suspension.

Events that are associated with the use of a veterinary medicinal product in human as part of a

suicidal attempt should not be considered an emerging safety issue.

In some cases, emerging safety issues may concern or involve a quality issue or specific batch recalls may be necessary. However, a batch recall on itself is not considered an emerging safety issue.

When notifying an emerging safety issue, the marketing authorization holder should describe the safety issue, the source(s) of information, actions taken or any planned actions with timelines, and should provide any relevant documentation available at the time of initial notification. Any further information relevant to the issue should be provided to PVGA as soon as it becomes available.

Upon being notified of an emerging safety issue, PVGA will promptly assess the urgency and potential impact of the issue and agree on appropriate next steps and the potential regulatory procedure to address the matter raised.

The marketing authorization holder should collaborate with PVGA in the assessment of emerging safety issues.

2.2.5 Signal validation

Signal validation is the first step in analyzing a detected signal. Signal validation means evaluating the initial data supporting a signal, in order to verify that the available information contains sufficient evidence demonstrating the existence of a new potential causal association, or a new aspect of a known association, and therefore justifies further analysis.

As a minimum, it is expected that the marketing authorization holder should check at this step that:

- the event occurred after exposure to the medicinal product (i.e. there is a temporal association);
- the signal is not based on duplicate reports;
- the suspected adverse event is not already adequately reflected in the current product information.

Even if certain terms are not explicitly included in the product information, it may be the case that the observed clinical signs are already covered by the text included in the product information.

Other information that can be checked at this step is, for example, if the signal concerns an increase in the number of reports involving an expected event, reflected in the product information, that this increase is not related to an increase in sales volumes or other external factors that might stimulate the reporting (e.g. increased media attention, etc.).

The signal validation step acts as the first quality check of the cases and the evidence supporting a signal in light of any previous experience, e.g. previous cases reported, previous analyses done on the same issue, any information available on the same issue in other regulatory procedures, etc. Non-validated signals do not require any further in-depth assessment and should not be recorded in the pharmacovigilance database.

2.2.6 Signal assessment

Once a signal is validated, further assessment shall be performed by the marketing authorization holder.

The assessment of the signal should be as comprehensive as possible in order to reach a high-quality decision and signal outcome. The assessment should include a cumulative review of all available evidence (i.e. not only the cases received during a certain reporting period, but all previously reported similar cases). In this cumulative review, the available pharmacological, pre-clinical, clinical, and epidemiological data from all sources should be reviewed, as applicable, in order to conclude on a potential causal association between the veterinary medicinal product and the concerned suspected adverse event.

Some elements regarding the clinical relevance of the reaction, such as the seriousness, severity, the outcome, and reversibility, are important in the assessment of a signal.

The following elements should be considered, as applicable, when performing the assessment:

- Total number of cases (after exclusion of duplicates), and from those, the number of supportive cases, e.g. cases showing a compatible time to onset, positive de- or rechallenge, lack of potential alternative causes, assessed as possibly related by the reporting veterinarian or healthcare professional, with supportive results of relevant investigations.
- Incidence.
- Additional cases reported with related terms (e.g. other terms indicating clinical complications or different stages of the same reaction).
- Consistency of the evidence across cases (e.g. consistent time to onset, pattern with repeated observations of an association).
- Quality of the data and their supporting documentation.
- Dose-reaction relationship.
- Possible mechanism based on biological and pharmacological plausibility.
- Disproportionality of reporting, if applicable.
- Potential drug-drug interactions.

Additional sources of information may provide further evidence for or against a potential causal association and may be considered:

- Experimental, non-clinical data and clinical trial data.

- Findings regarding similar cases in the scientific literature, including information on substances of the same class of veterinary medicinal products.
- Information on the epidemiology of the adverse reaction or the underlying disease.
- Databases with larger datasets, if available.
- Information from other regulatory authorities worldwide.

2.2.7 Recommendation for action by the marketing authorization holder

As a result of the assessment of a signal, the marketing authorization holder should conclude whether the available evidence reviewed supports a potential causal association, or not, between the veterinary medicinal product or active substance concerned and the suspected adverse event and therefore, if this adverse event constitutes a new risk, including a new aspect of a known adverse reaction. If it is concluded that the safety profile of the product or active substance has changed, the need for additional risk minimization measures and any other regulatory actions should be considered, including a variation to the terms of the marketing authorization.

This leads to the following possible actions to be considered, as appropriate, by the marketing authorization holder following signal assessment;

- The available evidence supports a causal association resulting in a change to the benefit-risk or a new risk:
    - The new risk is considered an emerging safety issue (see section 2.4.2).
    - Notify within 45 calendar days with a proposal for the necessary action and any risk minimization measures as applicable.
- The available information suggests that a potential causal association is at present unlikely;
    - Signal refuted, no further action besides routine pharmacovigilance.
- The available information is insufficient to conclude on a potential causal association at present, but further information is expected to provide evidence that could change this conclusion:
    - Close monitoring (see section 2.7.2).
    - A post-marketing surveillance study is required to further investigate the issue (see section 2.7.3).

a) Signal is refuted

When the available information suggests that the observed adverse events are more likely associated with other factors not related to the exposure of the veterinary medicinal product, e.g. to the underlying condition of an animal, exposure to other medicines, etc. the signal can be refuted and closed without the need for any additional regulatory actions (i.e. routine pharmacovigilance activities will continue to be performed). In this case, the signal could still be reopened in the future should any new relevant information become available.

b) Close monitoring

In some cases, it might be decided that the signal should not be closed and some further follow-up (i.e. close monitoring) is required. In this case, the marketing authorization holder should report at each yearly due date on the status of the signals under close monitoring. This approach should be followed for signals where the overall available information is insufficient to exclude a potential association with exposure to the veterinary medicinal product. Shorter reporting time-periods for the close monitoring of certain signals may be set by the relevant competent authority(ies) (e.g. 6-months).

For signals under close monitoring for an extended period (e.g. more than 2 years), stopping of the close monitoring can be proposed at the time of the yearly submission (i.e. due date) with a detailed justification.

c) Post-marketing surveillance study

In some cases, it might be concluded that spontaneous data are not enough to evaluate a certain potential risk identified through signal management. Additional data collection may be needed to conclude on the potential causal association with the veterinary medicinal product. In these cases, the marketing authorization holder may propose to voluntarily conduct a post-marketing surveillance study. In exceptional cases, a post-marketing surveillance safety study may also be requested by the Egyptian regulatory authority.

2.2.8. Quality management system requirements

Signal management is considered a critical process. Marketing authorization holders should make sure to document their signal management process, including detailed policies, processes and procedures, to ensure that the system functions properly and effectively, that the roles, responsibilities and required tasks are clear and standardized, that these tasks are conducted by staff with appropriate qualifications and expertise and that there are provisions for appropriate control and, when needed, improvement of the system. A quality management system should be applied to all signal management processes. Detailed procedures for this quality management system should be developed, documented, and implemented. This includes the rationale for the method and periodicity of signal detection activities.

Through a tracking system, all organizations should keep an audit trail of signal management activities, allowing traceability (i.e. recording of dates and confirmation of timeliness) and process control of the details of all steps of signal management, including analyses, decisions, and rationale.

These elements should be available for inspection.

When the marketing authorization holder opts to use its own database for signal detection and analysis, detailed description of the data collection process, the data tables, and available queries shall be made available on request or at the time of pharmacovigilance inspections.

The organizational roles and responsibilities for the activities, including maintenance of documentation, quality control and review and for ensuring corrective and preventive action should be assigned and recorded. Each organization should ensure that staff members are specifically trained in signal management activities in accordance with their roles and responsibilities.

3-Individual case safety report collection, management, and submission:

3.1. Introduction:

This module of the guideline on veterinary good pharmacovigilance practices (VGVP) brings together general guidance on the requirements, roles, activities and procedures related to collection and recording of suspected adverse events for veterinary medicinal products occurring in Egypt.

Suspected adverse event reporting is the primary information source for post-authorization safety monitoring for medicinal products, including veterinary medicinal products, and provides most of the data for the evaluation of the benefit-risk profile of a medicinal product.

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

Marketing authorization holders shall report ICSRs to the General Administration of Pharmaceutical Vigilance at EDA.

3.2. Structures and processes:

3.2.1. Collection of suspected adverse events:

PVGA and MAHs must actively promote the reporting of suspected adverse events (SAEs) associated with authorized veterinary medicinal products. This applies to events from:

- *Unsolicited sources (e.g. spontaneous reports from veterinarians, farmers, or the public).*
- *Solicited sources (e.g. post-marketing studies, surveys, or organized data collection).*

Both PVGA and MAHs must implement robust systems to collect, collate, and manage suspected adverse events (SAE) reports effectively. All collected data should be verified for completeness, entered into the national pharmacovigilance system (VigiFlow Egypt - Veterinary Module) and handled in accordance with Good Pharmacovigilance Practices.
The suspected adverse events include:

1. Unfavorable or unintended reaction in any animal to a veterinary medicinal product.
2. Lack of efficacy (with or without correct usage per the Summary of Product Characteristics).
3. Environmental incident after product administration.
4. Noxious reaction in humans exposed to a veterinary medicinal product.
5. Residue detection in animal-origin products exceeding the maximum residue limit, even after withdrawal period.
6. Suspected transmission of infectious agents via a veterinary medicinal product.
7. Adverse reactions in animals to medicinal products for human use.

The MAH is expected to validate all adverse events reported by veterinarians and other healthcare professionals and the general public to ensure, prior to reporting to EDA, that the minimum information required is included in the report (see Section 3.2.2 Validation of suspected 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 EDA. All available information relevant to the evaluation of the adverse reaction should be provided.

Unsolicited reports:

a) Spontaneous reports:

A spontaneous report is an unsolicited communication by a veterinarian or other healthcare professional or a member of the general public to PVGA, marketing authorization holder or other organization (e.g. regional pharmacovigilance center, poison control center) that describes one or more suspected adverse events observed in an animal or a number of animals or a human or in the environment following exposure to one or more medicinal products. It does not derive from a study or any organized data collection systems.

b) Literature reports:

Scientific literature is an additional useful source of information for monitoring the benefit-risk

balance of veterinary medicinal products, particularly in relation to the detection of new safety signals, emerging safety issues and potentially important efficacy or environmental issues. Marketing authorization holders are expected to review scientific literature in line with their internal procedures using relevant databases for information related to their authorized veterinary medicinal products.

Marketing authorization holders should conduct such a review at least once a year, where necessary more frequently based on a risk-based approach, and ensure that any identified suspected adverse event reports are recorded and reported to EDA.

The literature review should be performed in a thorough and well-structured manner with regard to adequacy of search criteria used (e.g. key words, search terms) and databases searched, to ensure the completeness of search results. Marketing authorization holders should ensure that procedures are in place to monitor publications in relevant peer-reviewed scientific journals. In case the marketing authorization holders become aware of publications in non-peer-reviewed local journals, the suspected adverse events identified in these publications should be reported as well. Marketing authorization holders should have procedures in place on how the publications in non-peer-reviewed local journals are brought to the attention of their safety department as appropriate.

c) Reports from other non-medical sources, internet or digital media:

If a marketing authorization holder becomes aware of a report of suspected adverse reactions originating from a non-medical source, for example the lay press or other media, it shall be managed as a spontaneous report. Every attempt shall be made to follow-up the case to obtain the minimum information that constitutes a valid ICSR.

Solicited reports:

All suspected adverse event reports originating from clinical studies for authorized veterinary medicinal products (e.g. clinical studies conducted to investigate a new indication, a new species, and new methods of administration or new combinations) and post-marketing surveillance studies related to veterinary medicinal products. Reports of suspected adverse reactions obtained from any of these data collection systems shall not be considered spontaneous.

With regard to the submission as ICSRs, solicited reports shall be classified as study reports. They shall have an appropriate causality assessment to consider whether they refer to suspected adverse reactions and therefore meet the minimum validation criteria.

ICSRs shall be submitted in line with the time frames and modalities.

3.2.2. Validation of suspected adverse event reports:

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

1. An identifiable primary reporter or source:

The primary reporter is the person who first reports the suspected adverse event and corresponds to the primary source of information. Characterized by parameters such as qualification (e.g. veterinean, pharmacist, other healthcare professional, lawyer, consumer or other non-healthcare professional), name, initials, or address (e.g. reporter's organization, department, street, city, state or province, postcode, country, email, phone number). Local data protection laws might apply. Contact details for the reporter shall be recorded to facilitate follow-up activities. However, if the reporter does not wish to provide contact information, the ICSR shall still be considered valid as long as the notified organization is able to confirm the case directly with the reporter.

To enable duplicate detection activities, all parties providing case information or approached for case information shall be recorded in the ICSR (not only the initial reporter).

In case of more than one identifiable reporter, the reporter who provides the most pertinent information related to the suspected adverse event report should be considered as the primary reporter and any other reporter should be recorded as "other reporter".

2. Details of identifiable affected animal(s) or human(s) or environment:

Species (including "human" when applicable) and number of animals or individuals affected is the minimum information required for a valid suspected adverse event report. The number (known or estimated) of animals or individuals affected should also include indirectly exposed animals or individuals, e.g. offspring from animals or individuals treated during pregnancy, suckling animals or infants, animals or individuals affected from infectious spread or through commingling (e.g. licking topical medicinal products). For environmental incident(s) ,the following information should be recorded in addition to the animal species and number of animals affected: the type of information in the suspected adverse event report should be "Other" and the relevant VeDDRA term(s) should be selected. Any specific information regarding environmental incidents should be recorded in the case narrative.

3. One or more medicinal product(s)/active substance(s) (veterinary or human):

Details of all medicinal product(s) to which the animal(s), human(s) or the environment were exposed prior to the occurrence of adverse events, should be recorded.

4. Suspected adverse event(s) details:

Clinical signs (including abnormal laboratory findings), diagnosis, or symptoms (for adverse event(s) in humans). Any of the above should be recorded and the relevant VeDDRA terms

should be selected. The number (estimated or known) of animals affected by each adverse event should be recorded against the relevant VeDDRA term. The date of onset of the suspected adverse event should also be recorded if available. Reasonable efforts should be made in order to clarify details of the event(s).

Case narrative:

The case narrative is very important and should contain all known relevant clinical and related information as provided by the primary reporter. This information should also be recorded using the VeDDRA terminology, including animal or human or environment details, exposure or treatment details. The course of suspected adverse event(s) and a description of the suspected adverse event(s) including the outcome, diagnosis, and any other information regarding the suspected and concomitant medicinal products (e.g. laboratory test results, necropsy findings) should also be recorded. 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 (e.g. body weight gain, Feed Conversion Ratio (FCR), body growth). The case narrative should serve as a complete and comprehensive case report, presented in a logical sequence, ideally in chronological order. The use of abbreviations and acronyms should be avoided.

The following elements, if available, are important for the evaluation of the report:

1. Description of suspected adverse event(s) including site and severity (intensity of the adverse event) and observed clinical signs.
2. Start date or onset of suspected adverse event.
3. Stop date or duration of suspected adverse event.
4. Specific measures taken to treat the observed suspected adverse event.
5. Number of animals showing clinical signs.
6. Number of animals dead.
7. De-challenge information (e.g. any obvious effect of removal of treatment).
8. Re-challenge information (e.g. any obvious effect of re-introduction of treatment).
9. If available, the following information should be provided:
    9.1. Number of treated animals alive with clinical sequel.
    9.2. Number of treated animals recovered.
10. The description of the content of any attached file(s), such as supplemental documents that contain significant information for the scientific evaluation of the case on e.g. pathology, radiology, clinical chemistry, virus sequencing, other laboratory results or literature articles. The processing of personal data should be performed in accordance with data protection legislation while ensuring that personal data is anonymised.

3.2.3. Suspected adverse events following the use of medicinal products for human use in animals:

PVGA should proactively engage with veterinarians and healthcare professionals to encourage reporting of suspected adverse events (SAEs) in animals resulting from the use of human medicinal products. These events, whether due to intentional off-label use, accidental exposure, or environmental contact, should be collected and recorded in the Egyptian pharmacovigilance database. This enables PVGA to issue safety alerts to veterinarians or the public when needed. While marketing authorization holders (MAHs) registering human-use products are not legally required to report such events in animals, if a case involves both veterinary and human products, the report must include complete information on all products involved.

3.2.4. Information related to pre-mixes and medicated feeding stuffs:

When pre-mixes, which have been incorporated in medicated feeding stuffs, are related to a suspected adverse event in animals or humans, 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 to include, when available.

3.2.5. Investigation of fatal outcome:

In the event of a fatal outcome following the use of a veterinary medicinal product, the cause of death—if known—should be clearly stated, along with an assessment of its possible relationship to the suspected adverse event, ideally by the attending veterinarian. Where available, necropsy findings should be included, supported by a description of the investigative procedures performed and a summary of any relevant sample analyses to aid in evaluating the case.

3.2.6. Suspected adverse event(s) in humans:

Information about any suspected adverse event(s) in humans with veterinary medicinal products, whether occurring in conjunction with the treatment of animals, the handling of veterinary medicinal products or following exposure through the environment, shall be reported.

For each suspected adverse event in humans, information on the items below should be included in addition to the minimum information for a valid suspected adverse event report, in order to

facilitate a full evaluation.

Additional information facilitating a full evaluation:

- Date the veterinary medicinal product(s) was (were) used or date of exposure to veterinary medicinal product(s).
- Date of suspected adverse event(s) in humans.
- Nature of exposure, including type of exposure, e.g. inhalation, injection, ingestion or dermal, and duration of exposure.
- Outcome of suspected adverse event(s) in humans, e.g. extent of recovery, specific treatment required.
- The conclusion/comments of the marketing authorization holder or national competent authority on the suspected adverse event(s) in humans provided in the case narrative as applicable.
- Animal and treatment data, e.g. method of administration, administration site, number and species of animals being treated.

3.2.7. Reports on investigations of the validity of a withdrawal period:

When residues of veterinary medicinal products are detected in animal-origin products (e.g., meat, milk, eggs) despite following the stated withdrawal period, it is critical to investigate and report the event to the Pharmacovigilance General Administration (PVGA). These reports contribute to ensuring food safety and maintaining public and animal health.

In addition to the **minimum criteria for a valid ICSR**, the following details must be reported:

1. Withdrawal Period Applied
    - Specify the withdrawal period observed before the product was harvested or marketed.
2. Date of Detection of Residues
    - When the residue was detected, typically through a laboratory or inspection authority
3. Residue Level Detected
    - Measured concentration of the active substance or marker residue (e.g., mg/kg or ppb).
4. Location of the Case
    - Specify the **governorate** or **veterinary district** within Egypt where the violation occurred.
5. Analytical Method Used
    - Name the testing method (e.g., HPLC, LC-MS/MS, ELISA) used

6. Other Relevant Information
    - Examples: species affected, batch number of the product, administration method, farm management practices, concurrent treatments, potential cross-contamination.
7. Steps Taken by the MAH
    - Describe corrective actions, such as:
        - Investigation reports
        - Sampling and analysis
        - Internal CAPA (Corrective and Preventive Action)
        - Notifications to PVGA and distribution partners

Regulatory Notes

- MAHs must **report such events within 30 calendar days** from the date of becoming aware.
- Reports should be sent to **PVGA** via the established electronic submission route or paper-based forms (if applicable).

3.2.8. Suspected transmission of an infectious agent via a veterinary medicinal product:

Any organism, virus, or infectious particle, pathogenic or non-pathogenic, is considered an infectious agent. Unintended transmission of an infectious agent may be suspected from clinical signs in animals, clinical signs and symptoms in humans, or laboratory findings indicating an infection in animal(s) or human(s) or organism(s) exposed to a veterinary medicinal product.

Emphasis should be on the detection of infections/infectious agents known to be potentially transmitted via a veterinary medicinal product, but the occurrence of unknown agents should also always be considered.

In the context of evaluating a suspected transmission of an infectious agent via a veterinary medicinal product, care should be taken to discriminate, whenever possible, between the **cause** (e.g. injection / administration) and the **source** (e.g. contamination) of the infection and the clinical conditions of the animal(s) or human(s) or organism(s) at the time of the infection (immunosuppressed/vaccinated).

Confirmation of contamination (including inadequate inactivation/attenuation of infectious agents as active substances) of the concerned veterinary medicinal product increases the evidence for transmission of an infectious agent and may therefore be suggestive of a quality defect for which the relevant procedures should be applied.

3.2.9. Suspected adverse events involving suspected or confirmed quality defects:

It is important that suspected or confirmed quality defects of veterinary medicinal products are handled according to the relevant procedures and guidelines.

Suspected adverse event reports involving suspected or confirmed quality defects shall be to EDA without delay and no later than within 30 days from their date of receipt. The relevant VeDDRA terms should be selected.

3.2.10. Handling of duplicate reports:

- *Receiving and Recording Reports:*

In Egypt, both the Pharmacovigilance General Administration (PVGA) and Marketing Authorization Holders (MAHs) are authorized to receive and record suspected adverse event (SAE) reports related to veterinary medicinal products in the Egyptian pharmacovigilance database.

SAE reports may be submitted:

- By **multiple sources**, such as veterinarians, farmers, or the general public.
- Through **multiple channels**, including:
  - ✓ Online reporting forms
  - ✓ Email
  - ✓ Telephone
  - ✓ Regional reporting centers

- *Risk of Duplicate Reporting:*

Due to the variety of reporting sources and methods, **the same suspected adverse event** may be:

- Submitted by **more than one MAH** (e.g. if multiple products are suspected).
- Reported **to both PVGA and MAHs** separately.
- Received **through more than one reporting channel** (e.g. phone and online form).

- *Preventing and Managing Duplicates:*

To support accurate duplicate detection:

- MAHs and PVGA must use standardized terminology, specifically:
  - **VeDDRA** for clinical signs and reaction terms
  - Standard product and substance naming conventions
  - **Uniform formats** for animal and event data
- Each SAE report entered should be:
  - As complete and detailed as possible
  - Checked for **existing records** involving the same case

- Clearly marked as **“initial”** or **“follow-up”** where applicable

- Where a potential duplicate is identified:

PVGA and/or MAHs must **reconcile** and **link the reports** using appropriate fields.

3.2.11. 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 following five categories of causality can be selected:

- Category 1: Probable.
- Category 2: Possible.
- Category 3: Unclassifiable/Unassessable (events where insufficient information was available to draw any conclusion).
- Category 4: 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
7. Products to the development of an adverse event (dose-effect relationship)

For inclusion in category "1" (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) such reports can only be classified as "2" (possible), "3" (unlikely), "or "4" (unclassifiable/unassessable).

For inclusion in category "2" (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 "1".

For inclusion in category "3" (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 "4" (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.

3.2.12. Follow-up:

Marketing authorization holders are responsible for the pharmacovigilance of their veterinary medicinal products and therefore primary responsibility for follow-up of suspected adverse event reports rests with the marketing authorization holder of the concerned product. The primary receiver of a suspected adverse event report, marketing authorization holder, should make reasonable efforts to communicate with the primary reporter as necessary to enable analysis of suspected adverse event(s), including the results of appropriate diagnostic tests. Where considered appropriate, the marketing authorization holders are encouraged to support the veterinarians with any additional investigations (e.g. necropsy, laboratory results) required. All available information relevant to the evaluation of the suspected adverse event should be provided. Follow-up activities should be documented.

3.2.13. 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 fulfills 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 organization having a contractual arrangement with the MAH concerning conduct of pharmacovigilance.

3.2.14. Submission of ICSRs:

Reception of ICSRs

The marketing authorization holder shall submit all ICSRs that occur in Egypt (i.e. domestic ICSRs) to the General Administration of Pharmaceutical Vigilance.

ICSRs shall be submitted electronically.

Pharmaceutical companies shall report ICSRs through:

• E-mails to: pv.vet@edaegypt.gov.eg

4- Pharmacovigilance Inspection

4.1 Introduction:

This Chapter provides guidance on the planning, conduct, reporting and follow-up of pharmacovigilance inspections in Egypt, and outlines the role of the different parties involved.

General guidance is provided under structures and processes section, while operation in Egypt section covers the overall operation of pharmacovigilance inspections in Egypt.

The verification of compliance of marketing authorization holders with the legal requirements regarding pharmacovigilance through risk-based controls on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products is of fundamental importance.

For marketing authorization holders of veterinary medicinal in Egypt, it is the responsibility of EDA to verify, that the marketing authorization holder for the veterinary medicinal products satisfies the national pharmacovigilance requirements.

As part of controls EDA has the power to perform pharmacovigilance inspections of:

- Holders of a marketing authorization for a veterinary medicinal product;
- Its qualified person responsible for pharmacovigilance (QPPV).
- The representative(s) responsible for the reporting of suspected adverse events.
- Any third party carrying out pharmacovigilance activities in whole or in part, on behalf of, or in conjunction with the marketing authorization holder.

EDA shall ensure that all pharmacovigilance system master files are regularly checked and that the respective pharmacovigilance systems are correctly applied.
Regular checks of pharmacovigilance system master file requirements, as part of controls, may be used to support the risk-based approach to define the frequency of pharmacovigilance inspections.

The result of inspection shall be communicated to the marketing authorization holder, the QPPV and, if applicable, a third party to whom pharmacovigilance tasks have been contracted out to.

The marketing authorization holder will be given the opportunity to provide a response to the findings identified. This response should include a root cause analysis, further assessment, and corrective and preventative actions for each finding. The results of pharmacovigilance inspections shall be recorded by EDA.

The frequency of inspections should be determined by EDA taking into account the intrinsic risks and information indicating non-compliance.

This approach allows EDA to set up inspection programs and allocate resources to areas where the risk is the highest.

The scope of this Module is to provide general guidance on the planning, conduct, reporting, follow-up and operation of pharmacovigilance inspections in Egypt for monitoring of Marketing Authorization Holder compliance with pharmacovigilance obligations.

4.2. Structures and processes of inspections:

4.2.1. Sites to be inspected

The site where the pharmacovigilance system master file is located will be the primary site selected for inspection. Inspection of other sites may also be requested if necessary, to verify the conduct of specific pharmacovigilance activities that cannot be inspected at the pharmacovigilance system master file location.

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

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

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

Third parties that form part of a pharmacovigilance system should be inspection-ready and should accept to be audited and inspected, as necessary, and this should be reflected in the relevant agreements.

4.2.2. Inspection Planning:

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

The frequency and extent of inspections shall be appropriate to the potential risks associated with the respective veterinary medicinal product and the inspected party.

As a general approach, a marketing authorization holder should be inspected regularly, and the inspection frequency will be adjusted on the basis of risk-based considerations in accordance with the factors listed in this section.

In order to ensure that inspection resources are used in an efficient way, the scheduling and conduct of inspections will be driven by the preparation of inspection programs by EDA. Sharing of information and communication between inspectors and assessors within EDA is important to ensure successful prioritization and targeting of these inspections.

Risk-based controls and inspections shall be carried out by EDA taking account of, as a minimum, the intrinsic risks associated with the activities carried out by the inspected entity and the location of their activities, the past record of compliance based on the results of previous controls, where applicable, any information that might indicate non-compliance and the potential impact of non-compliance on public health, animal health, animal welfare and the environment.

Factors which may be taken into consideration, as appropriate, by EDA when establishing risk-based pharmacovigilance inspection programs include, but are not limited to:

- Inspection related factors:
  - Compliance history identified during previous pharmacovigilance inspections or other types of inspections (good clinical practices (GCP), good manufacturing and distribution practices (GMP/GDP), good laboratory practices (GLP)).
  - Re-inspection date recommended by the inspectors or assessors as a result of a previous inspection.
- Product related factors:
  - Product(s) with potential higher risk to human or animal health or the environment.
  - Product(s) with additional pharmacovigilance risk-management measures
  - Product(s) with large sales volume, i.e. products associated with large animal exposure in Egypt.
  - Product(s) with limited alternative on the market in Egypt.
- Marketing authorization holder related factors:

- Marketing authorization holder that has never been subject to a pharmacovigilance inspection.
- Marketing authorization holder with many products on the market in Egypt.
- Resources available to the marketing authorization holder for their pharmacovigilance activities.
- Marketing authorization holder with no previous marketing authorizations in Egypt.
- Negative information and/or safety concerns raised by EDA, other concerned bodies/medicines authorities outside Egypt or other areas (i.e. GCP, GMP, GLP and GDP).
- Changes in the marketing authorization holder organization, such as mergers and acquisitions.

- Pharmacovigilance system related factors:
  - Marketing authorization holder with sub-contracted pharmacovigilance activities (function of the QPPV, reporting of safety data, sub-contracting of pharmacovigilance system master file management, etc.).
  - Third parties employed to perform pharmacovigilance activities.
  - Change of QPPV since the last inspection.
  - Changes to the pharmacovigilance database(s), which may include a change in the database itself or associated databases, the validation status of the database as well as information about transferred or migrated data.
  - Changes in contractual arrangements with pharmacovigilance service providers or of the sites at which pharmacovigilance is conducted or in pharmacovigilance system master file management.
  - Other information available (e.g. assessment from other regulatory authorities outside Egypt.
  - Delegation or transfer of pharmacovigilance system master file management.

4.2.3. Inspection programs:

As a general approach, a marketing authorization holder shall be inspected on the basis of risk based consideration.

The establishment of inspection programs will ensure that Marketing authorization holders' pharmacovigilance system master files and the respective pharmacovigilance systems are inspected regularly, and that the inspection frequency is adjusted following risk-based approach in accordance with the factors in section 4.2.2 of this Module.

A risk-based program for routine inspections for marketing authorization holders in Egypt will be determined by EDA.

These inspections should be prioritized based on the potential risk to animal, public health and

the environment, considering the factors listed in section 4.2.2. This routine inspection program will be separate from any targeted inspections, but if a targeted inspection takes place it may replace the need for one under this program, dependent on its scope.

EDA is also responsible for the planning and coordination of pharmacovigilance inspections in order to ensure compliance with the national legislation and to verify the effectiveness of the marketing authorization holder‘s pharmacovigilance system.

4.2.4. Inspection types and inspection scope:

There are two main types of pharmacovigilance inspections, routine and targeted inspections, as described in the following sections of this Module. In addition, irrespective of whether an inspection is routine or targeted it can also fall in multiple other categories as described in other sections below.

The inspection scope will depend on the type of inspection (e.g. routine or targeted, system or product specific, re-inspection, remote inspection), on the objectives of the inspection as well as the coverage of any previous inspections by EDA.

- ✓ **Pharmacovigilance system inspections** are designed to review the procedures, systems, personnel, and facilities in place and determine their compliance with regulatory pharmacovigilance obligations. As part of this review, product specific examples may be used to demonstrate the operation of the pharmacovigilance system.
- ✓ **Product-related pharmacovigilance inspections** are focused on product-related pharmacovigilance issues, including product-specific activities and documentation, rather than a general system review. The general pharmacovigilance system may still be examined as part of a product-related inspection (e.g. the system used for that product).

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

- Information supplied in the pharmacovigilance system master file;
- Information concerning the functioning of the pharmacovigilance system, e.g. compliance data available from EDA such as the “National Pharmacovigilance and Safety reports database”;
- Specific triggers (see section targeted PV inspections below for examples of triggers).

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

1. Routine pharmacovigilance inspections:

Routine pharmacovigilance inspections are inspections scheduled in advance as part of inspection programs. There is no specific trigger to initiate these inspections, although a risk-

based approach to optimize supervisory activities should be implemented. These inspections are usually system inspections. One or more specific products may be selected as examples to verify the implementation of the system and to provide practical evidence of its functioning and compliance.

Particular concerns, e.g. raised by assessors, may also be included in the scope of a routine inspection, in order to investigate the specific issues.

Routine pharmacovigilance inspections shall examine compliance with EDA legislation and guidance, and the scope of such inspections shall include the following elements, as appropriate

- Adverse events for veterinary medicinal products:
  - Collecting, receiving and exchanging suspected adverse event reports from all types of sources, sites and departments within the pharmacovigilance system, including from those firms subcontracted by the marketing authorization holder to fulfill marketing authorization holder's pharmacovigilance obligations and departments other than their safety department.
  - Data transfer, data management, data coding, including the appropriate use of terminology (e.g. the use of medically important VEDDRA terms), suspected adverse event report validation and suspected adverse event report evaluation.
  - Follow-up of suspected adverse event reports.
  - Recording of adverse events according to the requirements and timeliness of such recording.
  - Record keeping and archiving of all relevant documents.
- Continuous benefit-risk balance monitoring:
  - Use of all relevant sources of information for signal detection (see VGVP Module on Signal Management).
  - Risk management system, including a process for monitoring the benefit-risk balance of products and performing signal management, processes to take appropriate action to minimize identified risks and communication plan.
  - The inclusion of post-marketing surveillance study data in continuous safety monitoring.
- Pharmacovigilance system:
  - QPPV role and responsibilities, e.g. access to the quality management system, the pharmacovigilance system master file, performance indicators, audit and inspection reports, and their ability to take action to improve compliance.
  - The roles and responsibilities of the marketing authorization holder in relation to the pharmacovigilance system.
  - Accuracy, completeness and maintenance of the pharmacovigilance system master file.

- Quality and adequacy of training, qualifications and experience of staff.
- Coverage and adherence to the quality system in relation to pharmacovigilance, including quality control and quality assurance processes.
- Fitness for purpose of computerized systems or other appropriate recording system for the management of adverse event data and pharmacovigilance related data.
- Contracts and agreements with all relevant parties appropriately reflect responsibilities and activities in the fulfillment of pharmacovigilance, and whether they are adhered to.
- Document management system, including archiving arrangements that ensure the safety and the timely availability of pharmacovigilance data and other relevant data for the pharmacovigilance system.
- Communication in accordance with good veterinary pharmacovigilance practices.

2. Targeted pharmacovigilance inspections:

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

Targeted inspections may arise when one or more of the triggers listed below are identified:

- Risk-benefit balance of the product:
  - Change in the risk-benefit balance where further examination through an inspection is considered appropriate.
  - Delays or failure to identify or communicate a risk or a change in the risk-benefit balance.
  - Communication of information on pharmacovigilance concerns to the general public without giving prior or simultaneous notification to EDA, as applicable.
  - Non-compliance or product safety issues identified during the monitoring of pharmacovigilance activities by EDA.
- Reporting obligations:
  - Delays or omissions in reporting.
  - Poor quality or incomplete reports.
  - Inconsistencies between reports and other information sources.
  - Failure to provide the requested information or data within the deadline specified by EDA.
  - Poor quality or inadequate provision of data to fulfill requests for information from EDA.
- Fulfillment of commitments:

  - Concerns about the status or fulfillment of commitments.
  - Delays or failure to carry out specific obligations relating to the monitoring of product safety, identified at the time of the marketing authorization.
  - Poor quality of reports requested as specific obligations.
- Inspections:
  - Delays in the implementation or inappropriate implementation of corrective and preventive actions.
  - Information such as non-compliance or product safety issues from other types of inspections (GCP, GMP, GLP and GDP).
  - Inspection information received from other authorities which may highlight issues of non-compliance.
- Others:
  - Concerns following review of the pharmacovigilance system master file.
  - Non-inspection related information received from other authorities, which may highlight issues of non-compliance.
  - Other sources of information or complaints.
  - Frequent changes in the location of the pharmacovigilance system master file and shared pharmacovigilance system master file may also be taken into account.

The scope of targeted inspections should depend on the specific trigger(s) and may include the QPPV involvement and awareness of product-specific issues, in-depth examination of processes, decision making, communications and actions relating to a specific trigger and/or product.

3. Announced and unannounced inspections:

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

4. Re-inspections:

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

5. Remote inspections:

These are pharmacovigilance inspections performed by inspectors remote from the premises of the marketing authorization holder or firms employed by the marketing authorization holder.

Communication mechanisms such as the internet or telephone may be used in the conduct of the inspection. For example, in cases where key sites for pharmacovigilance activities are located outside Egypt or a third party service provider is not available at the actual inspection site, but it is feasible to arrange interviews of relevant staff and review of documentation, including the safety database, source documents and pharmacovigilance system master file, via remote access. This approach may also be taken where there are logistical challenges to an on-site inspection during exceptional circumstances

(e.g. a pandemic outbreak or travel restrictions), in accordance with the guidance on Remote pharmacovigilance inspections of MAHs during a crisis situation - Points to consider. Such approaches are taken at the discretion of the inspectors and in agreement with the body commissioning the inspection. The logistical aspects of the remote inspection should be considered following liaison with the marketing authorization holder. Where feasible, a remote inspection may lead to a visit to the inspection site if it is considered that the remote inspection has revealed issues which require on-site inspection or if the objectives of the inspection could not be met by remote inspection.

4.2.5. Inspection follow-up:

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

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

4.2.6. Regulatory actions and sanctions:

In order to protect public health, animal health and the environment, EDA is obliged to ensure compliance with pharmacovigilance obligations. When non-compliance with pharmacovigilance obligations is detected, the necessary action should be judged on a case-by case basis. What action is taken should depend on the potential negative animal and/or public health impact of the non-compliance(s). Any instance of non-compliance may be considered for enforcement action. Action may be taken by EDA as appropriate. EDA shall take the necessary measures to ensure that a marketing authorization holder is subject to effective, proportionate and dissuasive penalties. In the event of non-compliance, possible regulatory options include, as applicable:

- Education and facilitation: EDA may communicate with marketing authorization holder representatives (e.g. in a meeting) to summarize the identified non-compliances, to clarify the legal requirements and the expectations of the regulator, and to review the marketing authorization holder's proposals for corrective and preventive actions;
- Inspection: non-compliant marketing authorization holders may be inspected to determine the extent of non-compliance and then re-inspected to ensure compliance is achieved;
- Warning letter, non-compliance statement or infringement notice may be issued stating the legislation and guideline that has been breached, reminding marketing authorization holders of their pharmacovigilance obligations or specifying the steps that the marketing authorization holder should take and in what timeframe in order to rectify the noncompliance and in order to prevent a further case of non-compliance;
- EDA may consider making public a list of marketing authorization holders found to be seriously or persistently non-compliant;
- Actions against a marketing authorization(s) or authorization application(s) e.g.:
    - Urgent safety restriction;
    - Variation of the marketing authorization;
    - Suspension or revocation of the marketing authorization;
    - Delays in approvals of new marketing authorization applications until corrective and preventive Actions have been implemented or the addition of safety conditions to new authorizations;
    - Product recalls e.g. where important safety warnings have been omitted from product information;
    - Action relating to marketing or advertising information;
    - Amendments or suspension of studies due to product-specific safety issues;
    - Financial penalties, usually fixed fines or based on company profits or levied on a daily basis;
    - Criminal prosecution (in accordance with national legislation);

4.2.7 Qualification and training of inspectors:

Inspectors who are involved in the conduct of pharmacovigilance inspections requested by EDA should be officials and follow the provisions of EDA. It is recommended that inspectors are appointed based on their experience and requirements defined by EDA. The inspectors should undergo training to the extent necessary to ensure their competence for preparing, conducting and reporting inspections. If not acquired by their experience, they should be trained in pharmacovigilance processes and requirements in such way that they comprehend the different aspects of a pharmacovigilance system. Documented processes should be in place in order to ensure that inspection competencies are maintained. In particular, inspectors should be kept updated with the current status of pharmacovigilance legislation and guidance. Training and experience should be documented individually and evaluated according to the requirements of the applicable quality system of EDA

EDA shall have procedures or arrangements in place to ensure that staff performing controls and inspections are free from any conflict of interest.

4.2.8 Inspection procedures:

Pharmacovigilance inspections should be planned, coordinated, conducted, reported on, followed-up and documented in accordance with the legislative requirements, veterinary good pharmacovigilance practices and the procedures for pharmacovigilance inspections related to veterinary medicinal products that should cover, at least, the following processes:

- Sharing of information.
- Coordination of pharmacovigilance inspections in EDA.
- Coordination of third country inspections (including inspections of contractors in third countries);
- Preparation of pharmacovigilance inspections.
- Conduct of pharmacovigilance inspections.
- Reporting of pharmacovigilance inspections and inspection follow-up.
- Sanctions and enforcement in case of serious non-compliance.
- Recommendations on the training and experience of inspectors performing pharmacovigilance inspections.

In addition, guidance on marketing authorization holder preparedness for facilitation of pharmacovigilance inspections and controls should be made available.

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

5- Benefit Risk Evaluation Report / Addendum of clinical overview (ACO):

This document is intended to provide an update of the worldwide safety experience of veterinary medicinal product to PVGA at defined time points post-authorization.

A critical discussion addressing the current benefit/risk balance for the product on the basis of a consolidated version of safety/efficacy data accumulated since the initial MAA or the last renewal.

The Addendum to the Clinical Overview shall contain the following information:

- **Section titled "Introduction"**: a brief description of the purpose of the document specifying the time period covered and MAH and product details :
    1. MAH name
    2. The veterinary product name
    3. Version number if applicable
    4. The period covered by the document
- **Section I titled "Worldwide marketing authorization status"** overview of number of countries where the product has been approved and marketed worldwide and the dates of approval and launching & clarifies the marketing status in Egypt.
- Section II titled "Actions taken for safety reasons (worldwide)" :

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 report indicating scope, status and date should be given. Significant changes in the wording of the SPC should be explained, where of relevance to safety.

- Section III titled Significant changes made to 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 ACO. If evaluation of safety data leads to any proposed changes in the SPC.

- **Section IV titled "Meaningful differences between Reference safety information (RI)"** clarifying differences between Reference safety information (RI) (e.g.: current SmPC) & proposed SmPCs preferably in a tabulated form.

- Section V titled "Estimated Exposure and Use patterns":

Sales volume:

Each report should contain the number of doses/amount of veterinary products sold within the reporting period in Egypt 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 liters;
- ✓ Powder to be expressed in kilograms;
- ✓ Tablets to be expressed in numbers of tablets;
- ✓ Sprays to be expressed in liters 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:

- Authorized treatment regimen (daily dose (mg/kg) x duration of treatment (days)) as detailed on the authorized 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 document.

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 authorized 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 authorized 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).

- Section VI titled “Data in summary tabulations”:

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 document.

The analysis of the adverse events reported should be supported by tables or tabulations summarizing the main findings. It may be helpful, especially for ACOs 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 after exposure to animals treated by veterinary medicinal products
- ✓ Other pharmacovigilance fields:
  - Adverse events after use in non-target species
  - Potential environmental problems arising from the use of the veterinary products
  - 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 ACO (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 formulation (dosage form(s) and strength(s)), target species (if the veterinary medicinal product is authorized 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 ACO when relevant, and batch numbers should be identified in the review and the line listings, as available.

- Section VII titled " 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 other veterinary products) should be reported in ACO.

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 ACO.

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 ACO.

- Section VIII titled "Overall safety evaluation" :

The ACO 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 of the following):

- ✓ 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:

- o 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 organized 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 report, 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. Judgment 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).

- Section IX titled "Late-breaking information":

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.

General Notes on ACO submission:

- The previous license of the product in Egypt shall be submitted.
- The ACO document shall be signed by the QPPV/Clinical expert.
- The period covered by the ACO shall be with date format day/month/year as following:
  - ✓ **Starting date of the period covered by the ACO:** Date of initial marketing authorization or the date of the last renewal of the product.
  - ✓ **Data Lock Point of the ACO:** 90 days prior to submission of renewal file to Pharmaceutical Vigilance General Administration (1st submission)
- The stamped approved label shall be submitted in the ACO, besides the updated proposed SmPC (if any).
- All reference documents used to prepare such ACO that were used to define and classify the safety concerns and documents used to define the risk minimization activity shall be submitted, for example –but not restricted to
  - ✓ Search results

- ✓ Public assessment report.
- ✓ The SmPC of the reference product.
- ✓ Literatures

- In case the products were not marketed. MAH shall submit a statement (on MAH official paper) signed by CEO declaring that your product is not launched yet & never been marketed or sold by any tenders along with adequate justification.
- If not marketed, an estimated date for initially placing the product on the market

6- Risk management document:

It is recognized that at the time of authorization, information on the safety of a veterinary 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 populations remain to be identified during the clinical use of the product.

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.

EDA requires Applicants/MAHs to provide a document covering data about the risk management, when appropriate.

This document shall include the following:

1. The indication of the active ingredient.
2. Table reflecting the updated summary of safety concerns.
3. Table reflecting the proposed routine risk minimization activities, and how such routine activities will be sufficient to manage the product safety concerns.
4. Any other pharmacovigilance activities/additional if applicable.
5. The proposed SmPC of your product shall be submitted.

7- Submissions

Regarding files submitted in the context of Registration, the following is required:

- ICSRs (if found).
- Any emerging safety issues.
- PSMF and its summary for local MAHs or PSMF, its summary and PSSF and its summary for multinational companies.

Regarding files in the context of Re- Registration, the following is required:

- Addendum of clinical overview /Benefit-risk report
- PSMF and its summary for local MAHs or PSMF, its summary and PSSF and its summary for multinational companies.
- ICSRs (if found).
- Any emerging safety issues.
- Safety description document.

8- References

- Law No. 151/2019 for the establishment of EDA.
- Assistant Ministerial Decree No. 2/2010 for the regulations of pharmacovigilance and pharmaceutical products safety.
- Ministerial decree No. 368/2012 regarding the Egyptian pharmacovigilance center.
- EDA chairman Decree No.434/2022 for the regulations of re-registration of veterinary medicinal products
- EDA chairman Decree No.625/2024 for the regulations of registration of veterinary medicinal products
- Pharmacovigilance of veterinary medicinal products https://www.ema.europa.eu/en/veterinary-regulatory-overview/post-authorisation-veterinary-medicines/pharmacovigilance-veterinary-medicines
- Veterinary good pharmacovigilance practices (VGVP) https://www.ema.europa.eu/en/veterinary-regulatory-overview/post-authorisation-veterinary-medicines/pharmacovigilance-veterinary-medicines/veterinary-good-pharmacovigilance-practices-vgvp
- Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Collection and recording of suspected adverse events for veterinary medicinal products https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-collection-and-recording-

suspected-adverse-events-veterinary-medicinal-products_en.pdf

- Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Signal Management
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-signal-management_en.pdf
- Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-pharmacovigilance-systems-their-quality-management-systems-and-pharmacovigilance-system-master-files_en.pdf
- Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Controls and pharmacovigilance Inspections
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-controls-and-pharmacovigilance-inspections_en.pdf
- Guideline on veterinary good pharmacovigilance practices (VGVP) - Module: Glossary
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-veterinary-good-pharmacovigilance-practices-vgvp-module-glossary_en.pdf
- VeDDRA List of Clinical Terms for Reporting Suspected Adverse Reactions in Animals and Humans to Veterinary Medicinal Products
  https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/combined-veterinary-dictionary-drug-regulatory-activities-veddra-list-clinical-terms-reporting-suspected-adverse-events-animals-humans-veterinary-medicinal-products-rev16_en.pdf
- Saudi Guideline on pharmacovigilance for veterinary products
  https://www.sfda.gov.sa/sites/default/files/2020-01/PharmacovigilanceVeterinary-v1.pdf

Annex I: Templates:

Risk management document:

Active substance(s) (INN or common name):	
Name of Marketing Authorization Holder or Applicant:	
Name of the pharmacovigilance representative (if applicable)	
Number of pharmaceutical products to which this document refers:	
Product(s) concerned (brand name(s)):	

Version number of Risk management document:

Date of final sign off:

Table of content of risk management document:

- The indication of the product.
- Table reflecting the updated summary of safety concerns.
- Table reflecting the proposed routine risk minimization activities, and how such routine activities will be sufficient to manage the product safety concerns.
- Any other pharmacovigilance activities/additional if applicable.
- The proposed SmPC of your product shall be submitted.
- Indication of the product:
  - ✓ Current (if applicable) in Egypt:
  - ✓ Current of the reference pharmaceutical product:
  - ✓ Proposed (if applicable) in Egypt
  - ✓ That of the reference pharmaceutical product
- Table reflecting the updated summary of safety concerns:

Summary of safety concerns	
Important identified risks	
Important potential risks	
Missing information	

- Table reflecting the proposed routine risk minimization activities, and how such routine activities will be sufficient to manage the product safety concerns:

Routine risk minimization measures	
Additional risk minimization measures	

- Any other pharmacovigilance activities/additional if applicable:
- State any additional PV activities if applicable.
- The proposed SmPC of your product shall be submitted.