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The VGVP draft modules are released for consultation and may change further, pending the finalisation and publication of the Commission Implementing Regulation laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products.

Guideline on veterinary good pharmacovigilance practices (VGVP)

Module: Signal Management

Draft

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1. Introduction

This module of the guidelines on veterinary good pharmacovigilance practices (VGVP) brings together general guidance for marketing authorisation holders, national competent authorities and the European Medicines Agency (the "Agency") regarding signal management for veterinary medicinal products authorised in the European Union (EU).

Commission Implementing Regulation (EU) …/… of xxx, Article 17 (5) requires the Agency to publish guidance on best practice for signal management.

Regulation (EU) 2019/6 and the measures laid down in the Commission Implementing Regulation on veterinary good pharmacovigilance practice include provisions for signal management in the EU.

The objectives of this module are:

- to provide general guidance and requirements on scientific and quality aspects of signal management for veterinary medicinal products;
- to describe the roles, responsibilities, and procedural aspects of the EU signal management process for veterinary medicinal products.

This module is applicable to authorised veterinary medicinal products in the EU irrespective of the authorisation procedure (centralised or national procedure, including mutual recognition and decentralised), and including those used outside the terms of the marketing authorisation (i.e. off-label) and homeopathic products.

Unless stated otherwise, the guidance provided in this module applies predominantly to marketing authorisation holders but should also be considered by all organisations involved in the signal management process; national competent authorities, the coordination group, the Agency and the Commission.

The current guidance document on this module will be reviewed and updated in the future to reflect on the experience gained on the signal management process from all stakeholders.

This module should be read in conjunction with Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (the Regulation) and Commission Implementing Regulation (EU) …/... of XXX, laying down rules for the application of Regulation (EU) 2019/6 of the European Parliament and of the Council as regards good pharmacovigilance practice and on the format, content and summary of the pharmacovigilance system master file for veterinary medicinal products (the Implementing Regulation)< reference to the Commission Implementing Act to be completed when available>.

2. Structures and processes

2.1. Signal management activities by marketing authorisation holders

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

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. Where the

outcome of the signal management process identifies a change to the benefit-risk balance, a new risk, the marketing authorisation holder shall notify it without delay and no later than 30 calendar days, of receipt of the suspected adverse event report, to competent authorities, and where necessary submit a variation to the terms of the marketing authorisation in accordance with Articles 77(10) and 81(2) of Regulation (EU) 2019/6.

In case of an impact on the benefit-risk balance of the veterinary medicinal product concerned, on animal or public health, or on protection of the environment that is considered an emerging safety issue, identified by the marketing authorisation holder according to Article 58(10) of the Regulation, the marketing authorisation holder should notify it to the relevant competent authority(ies) without delay and no later than 3 working days following the identification of an emerging safety issue by the marketing authorisation holder (see section 2.3.1).

The signal management process should consist of, but not be limited to, the pharmacovigilance activities of signal detection, prioritisation, validation, assessment, and recommendation for action.

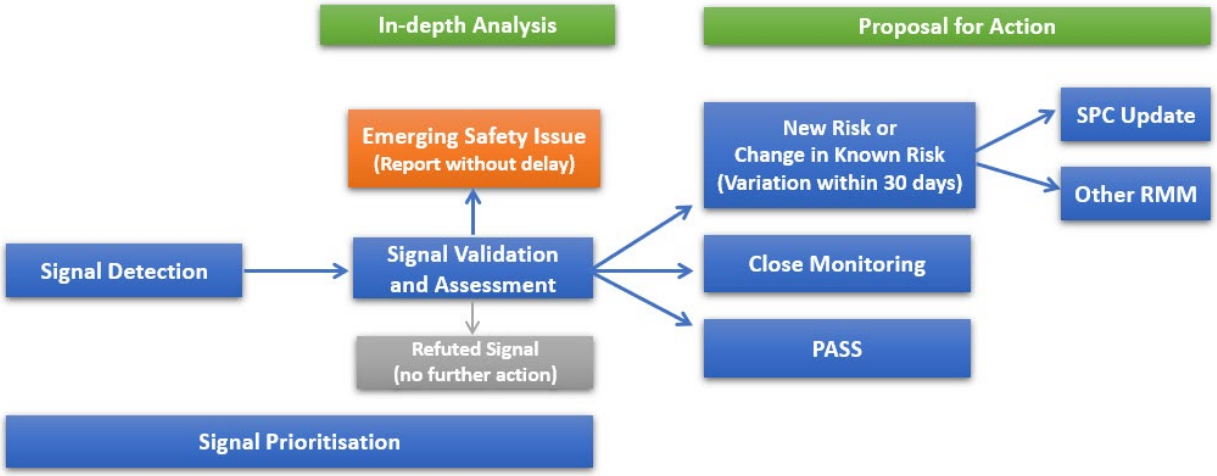

Figure 1. Overview of the signal management process for veterinary medicinal products

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 authorisation 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 (see Article 81(1) of Regulation (EU) 2019/6). Please also refer to the guidance on the collection and recording of suspected adverse events associated with veterinary medicinal products in the relevant VGVP module.

2.3. Signal prioritisation

Signal management should follow a risk-based approach which takes into account the type of medicinal product or active substance concerned and the nature and characteristics of the data, including but not limited to, the length of time on the market and the stability of the pharmacovigilance profile.

In order to avoid delaying the detection and management of certain signals that might require urgent attention, signal prioritisation should be performed throughout the whole signal management process, from deciding the periodicity of signal detection to the point of signal assessment. Prioritisation 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 minimisation in a timely manner. Clinical judgement and flexibility should be applied throughout the process.

The following subsections should be read in order of importance, with emerging safety issues (see section 2.3.1 of this document) and signals involving medically important terms (see section 2.3.2 of this document), being the most important issues to identify and prioritise.

2.3.1. Emerging Safety Issues

Any new information which might influence the assessment of the benefits and the risks of the veterinary medicinal product concerned according to Article 58(10) of Regulation (EU) 2019/6, and which may require urgent regulatory action and communication should be identified as an emerging safety issue. It should be reported to the relevant competent authority(ies), without delay and no later than 3 calendar days after identification of an emerging safety issue. Examples include:

- major safety issues identified in the context of ongoing or newly completed studies, e.g. an unexpectedly increased rate of fatal or life-threatening adverse events;
- major safety issues identified through 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 the EU, e.g. a restriction of the use of the veterinary medicinal product or its suspension.

In the context of Emerging Safety Issues, evidence of any serious[1] adverse events in human potentially associated with a veterinary medicinal product should be considered. However, events that include a veterinary medicinal product used as part of a suicidal attempt should not be considered an Emerging Safety Issue.

When a marketing authorisation holder in the EU becomes aware of an emerging safety issue from any source, they should notify the competent authority(ies) of the Member State(s) where the veterinary medicinal product is authorised and to the Agency. This should be done as soon as possible and no later than 3 calendar days after establishing that a validated signal or a safety issue from any source meets the definition of an emerging safety issue.

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

[1] Seriousness criteria used in human pharmacovigilance: An adverse reaction that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a birth defect

Upon being notified of an emerging safety issue, the national competent authorities or the Agency as appropriate 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. This may involve the consultation of the Incident review groups, if warranted (see Incident management plan for medicines for veterinary use[2]).

The marketing authorisation holder should collaborate with the Agency and national competent authorities in the assessment of emerging safety issues.

2.3.2. Signals involving Medically Important (MI) terms in VeDDRA

A list of Medically Important (MI) terms has been developed (Appendix 1) in VeDDRA. This list contains serious medical concepts at the level of VeDDRA preferred terms. It is intended to be used by marketing authorisation holders, the Agency and national competent authorities for signal prioritisation.

Reports involving MI terms should be always prioritised regardless of the absence of any statistical disproportionality measure (e.g. ROR[3]) or the number of cases reported (unless they are considered adequately reflected in the current product information). However, this does not mean that any report involving a MI term would concern a safety signal. As with any signals, usually more than a single report is required, although in exceptional circumstances, one single report can also generate a signal.

2.3.3. Prioritisation criteria for other types of signals

It is not uncommon for medicinal products used widely or in diseased animals that a relatively large number of potential signals are generated. Many such signals are false positive and further prioritisation is essential.

When prioritising other newly identified signals than emerging safety issues or signals involving MI terms, the following criteria, or a combination thereof, should be considered:

- Novelty of the medicinal product-event association. The focus should be on new associations or new aspects on 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.
- ROR value (not exclusive, i.e. a non-significant ROR does not exclude a potential signal).
- Public health, animal health and environmental protection implications.
- Species-specific events.

Results from previous analyses of identified signals can be used as a prioritisation 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 could be expected based on new relevant information.

[2] https://www.ema.europa.eu/en/documents/other/incident-management-plan-medicines-veterinary-use_en.pdf
[3] Reporting Odds Ratio (ROR) is a statistical measure based on the odds observed for an event occurring with a particular product compared to the odds observed of that same event in a reference data set of products.

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. social media.

2.4. Signal detection

If a marketing authorisation holder is responsible for the same or similar veterinary medicinal products in different Member States authorised through different authorisation procedures, signal detection and the signal management process shall be performed by grouping all relevant same and similar products.

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.

When using the Union Pharmacovigilance Database for signal detection, the marketing authorisation holder should make use of the available pre-defined queries in the Union Pharmacovigilance Database.

These include:

- Signal detection dashboard: Overview, Signal detection with RORs up to date 2 and up to date 1 (cumulative ROR), Static ROR evaluation.
- Signal evaluation dashboard: Animal Data (species/breed, age, weight analysis, pharmaceutical form, regional distribution, time to onset), Product information (pharmaceutical form, regional distribution), Product association (product used in association with another product), Associated VeDDRA terms (other reactions in the same Adverse Events reports).
- Incidence calculation queries.
- If needed, more tailored queries can be constructed based on the individual data elements.

The outputs of Union Pharmacovigilance Database are generally provided at the level of the active substance or combination of active substances. Outputs can also be generated on a product basis.

Marketing authorisation holders can use their own specific data analytical tools for the purpose of signal detection and assessment, when available. However, all marketing authorisation holders shall conduct at least one signal detection analysis per year in the Union Pharmacovigilance database (Article 17(7) of the draft Implementing Act).

2.5. Evaluation during signal validation and further assessment

The evaluation of the data supporting a detected signal can be divided in different steps.

Signal validation is the first step in analysing a detected signal. Signal validation allows 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 authorisation 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 only on duplicate reports;
- the suspected adverse event is not already adequately reflected in the current product information. Even if certain VeDDRA terms are not explicitly included in the product information it may occur that the observed symptoms 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.

Signal validation serves thus as a first quality check of the cases and the evidence supporting a signal in the context of any previous awareness, e.g. previous cases reported, previous analysis 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 Union Pharmacovigilance database.

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

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 cases). In this cumulative review, the pharmacological, pre-clinical, clinical, and epidemiological data from all available sources should be reviewed, as applicable, in order to conclude on a potential causal association between the medicinal product and the concerned suspected adverse event.

The assessment of the signal should be as comprehensive as possible and include all available data from different sources to increase the strength of the evidence in order to reach a high-quality decision and signal outcome, e.g. literature review, expert consultation, etc.

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 given that regulators may act on a precautionary principle and accept lower levels of evidence to recommend a regulatory action such as e.g. adding a warning in the product information.

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 (see section 3.5).
- Additional cases reported with related terms (e.g. other VedDRA 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 a 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 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 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.

2.6. Recommendation for action by the marketing authorisation holder

As a result of the assessment of a signal, the marketing authorisation 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 it this adverse event constitutes a new risk or a new aspect of a known risk. If it is concluded that the safety profile of the product/substance has changed, the need for additional risk minimisation measures and/or any other regulatory actions should be considered, including a variation to the terms of the marketing authorisation.

This leads to the following possible actions to be concluded, as appropriate, by the marketing authorisation 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 2.3.1 of this document).
  - Notify within 30 calendar days with a proposal for the necessary action (Article 81(2) of Regulation (EU) 2019/6).
  - Propose other actions and risk minimisation measures as applicable.
- The available evidence does not support a causal association at this moment:
  - Signal refuted, no further action besides routine pharmacovigilance.
  - Close monitoring.
  - A post-marketing surveillance study is required to further investigate.

2.6.1. Close monitoring

When the available evidence does not support a causal association between the medicinal product and the suspected adverse event, the signal can be closed without the need for any further regulatory action (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.

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 authorisation holder should report at each yearly signal detection submission on the status of the signals under close monitoring. Shorter reporting time-periods for certain signals may be set by the relevant competent authority (ies) (e.g. 6-months).

2.6.2. Post-marketing surveillance study

In some cases, it might be concluded that spontaneous data are not sufficient 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 authorisation holder may propose to conduct voluntarily a post-marketing surveillance study. In some cases, a post-marketing surveillance safety study may also be requested by the Agency or national competent authorities (Article 76(3) and (4) of Regulation (EU) 2019/6).

3. Operation of the EU network

Figure 2 below summarises the continuous signal management performed by marketing authorisation holders and the different types of submissions to competent authorities throughout a year of surveillance.

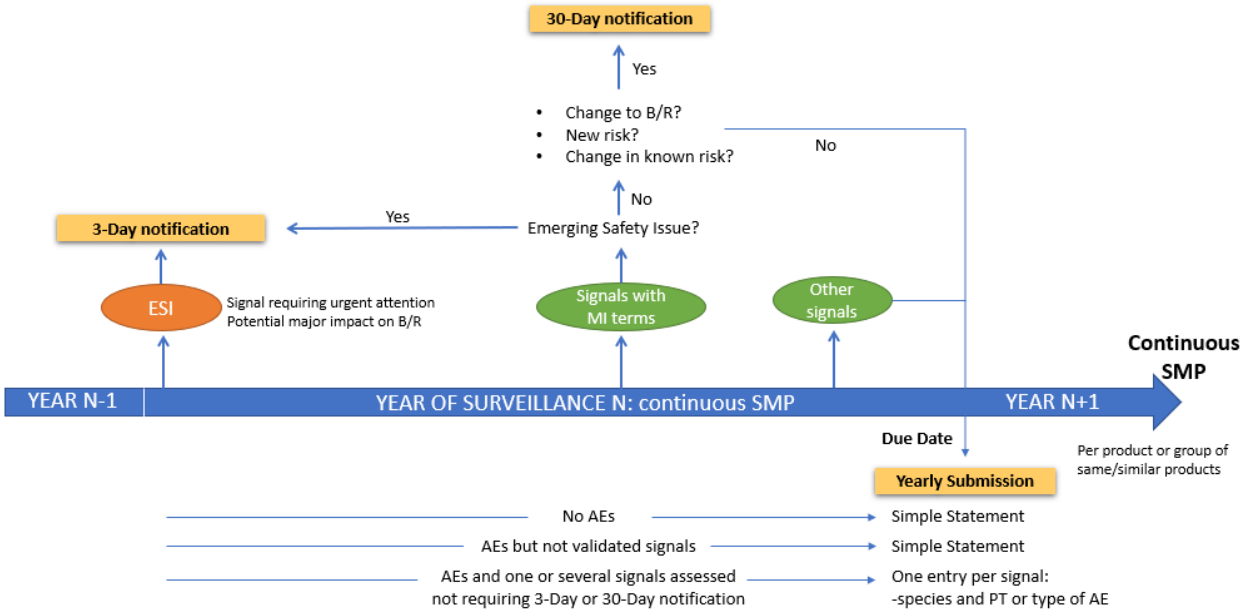

Figure 2. Overview of the continuous signal management process performed by MAHs throughout a year of surveillance

3.1. Roles, responsibilities, and procedural aspects

As stated in the legislation, marketing authorisation holders are responsible for the continuous monitoring of pharmacovigilance data and the assessment of the benefit-risk balance of their veterinary medicinal products (Articles 77(4) and 81 of Regulation (EU) 2019/6).

Signals detected by the marketing authorisation holder, regardless of the source, should be handled according to the principles outlined in this module. Some signals detected throughout the year will require more urgent attention by the regulators than others (see section 2.3 of this document). Accordingly, two separate procedures can be identified that will require evaluation by the competent authorities: the evaluation of signals that are submitted continuously throughout the year by the marketing authorisation holder which require regulatory action (including emerging safety issues and signals involving MI terms with a proposed regulatory action), and the evaluation of an annual statement by the marketing authorisation holder together with a summary of the validated signals

assessed throughout the year which did not require urgent attention or did not lead to any proposals for action as well as a conclusion on the benefit-risk balance of the veterinary medicinal product.

In order to facilitate and coordinate the evaluation by the competent authorities, due dates for submission of the annual statement on the benefit-risk balance (see section 3.2 of this document) and data on signals assessed throughout the year by the marketing authorisation holder (see section 2 of this document) will be set up for all active substances concerned. These will be defined annually, although more frequent than annual submission may be specified by the Agency (e.g. for specific new active substances (Article 81(2) referring to Article 42(2)(c)). At the time of submission, the marketing authorisation holders should submit and record the outcomes of the signal management process throughout the period in the Union Pharmacovigilance Database.

3.2. Recording of the outcome of signal management by the marketing authorisation holder

3.2.1. Signals which require reporting without delay

Emerging safety issues (see section 2.3.1 of this document), including those involving MI terms, should be notified as soon as possible and no later than 3 working days following the discovery of an emerging safety issue by the marketing authorisation holder. Emerging safety issues should be entered in the relevant module in the Union Pharmacovigilance Database with a description of the issue and the proposed actions.

For signals (except for those considered an emerging safety issue) where the marketing authorisation holder identifies a change to the benefit-risk balance or a new risk, that requires potential regulatory action, they should record the outcome of the signal management process into the Union Pharmacovigilance Database without delay and no later than 30 calendar days following the conclusion of the signal assessment. For this purpose, the signal should be entered in the signal module of the Union Pharmacovigilance Database.

The data to be entered should include the following fields:

- Administrative information: name of medicinal product(s), marketing authorisation holder, active substance(s).
- per signal: one entry specifying the species and the VeDDRA Preferred Term or type of adverse event, cumulative number or cases supporting the signal attached as line listing, the rationale for the decisions and the results of the signal assessment in an appropriate signal assessment report (*under development*) which should include a conclusion on the potential causal association and proposals for risk minimisation measures as necessary.

3.2.2. Annual reporting including annual statement

Marketing authorisation holders shall record at least once a year the results and outcomes of their signal management process in the Union Pharmacovigilance Database (Article 81 of Regulation (EU) 2019/6). This obligation applies for each veterinary medicinal product for which the marketing authorisation holder is responsible. As laid down in the Commission Implementing Regulation (<reference to be included upon publication>), at least annually, marketing authorisation holders shall record a conclusion on the benefit-risk balance of each of their products in the Union Pharmacovigilance Database and confirm that the signal management process has been conducted. This should be done regardless of any signals detected throughout the year.

The annual reporting shall take place by the due date set for each veterinary medicinal product. Signals falling under 3.2.1. of this document or any other signals reported already to the Union Pharmacovigilance database since the previous due date, do not need to be re-sent.

However, any other signals involving MI terms, should be recorded in the Union Pharmacovigilance database by the yearly due date, regardless of the conclusion of the assessment.

The data to be entered should include the following fields:

- Administrative information: name of veterinary medicinal product(s), marketing authorisation holder, active substance(s).
- Entry identified as "Yearly signal management", and due date.
- Per signal: one entry specifying the species and the VeDDRa Preferred Term or type of adverse event, cumulative number or cases supporting the signal attached as line listing, the rationale for the decisions and the results of the signal assessment in an appropriate signal assessment report (*under development*) which should include a conclusion on the potential causal association.

For signals that are considered under close monitoring and which were already submitted more than six months prior to the due date, the existing signal entry shall be updated by the due date with a summary of the new and similar cases received since the last update.

3.3. Incidence reporting by marketing authorisation

3.4. Targeted signal management by the competent authorities

This section is under development.

3.5. Transparency

In relation to the EU signal management of veterinary medicinal products, the following information will be published by the Agency on the European Medicines web-portal:

- Pharmacovigilance Working Party-veterinary (PhVWP), Committee for Medicinal Products for Veterinary Use (CVMP) and Veterinary Mutual Recognition Facilitation Group (CMDv) agendas.
- PhVWP-V, CVMP and CMDv recommendations.
- Cumulative list of signals discussed by the PhVWP-V, CVMP and CMDv with links to the relevant minutes.
- List of due dates for the submission of the yearly signal management outcomes for each veterinary medicinal product authorised in the EU, including homeopathic products.

4. Quality management system requirements

Signal management is considered a critical process. Marketing authorisation 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 standardised, 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 organisations 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.

When the marketing authorisation 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 organisational 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 organisation should ensure that staff members are specifically trained in signal management activities in accordance with their roles and responsibilities.

Definitions

Please refer to the VGVP Glossary (EMA/118227/2021) for relevant definitions.

Appendix 1. Medically Important (MI) terms list

As a guidance to prioritise the analysis of data during signal detection in the Union Pharmacovigilance database, a Medically Important (MI) terms list based on VeDDRA terms at the VeDDRA Preferred Terms level has been developed. This list should be used by the European Medicines Agency, EEA Member States, and market authorisation holders for signal prioritisation, as described in this module. The MI terms list contains VeDDRA Preferred Terms (PT) that identify serious medical concepts often causally associated with drugs across multiple pharmacological/therapeutic classes and should automatically be prioritised. However, if a MI term is already listed in the product information, limited assessment may be required (e.g., calculating if the observed incidence is similar to the expected incidence, etc.).

The MI terms list is not definitive and the absence of an event from the MI terms list does not exclude the event from analysis. PT terms on the MI terms list will be highlighted in the Union Pharmacovigilance Database to assist in the identification of these specific terms when performing signal detection. The content of the MI terms list may change as further experience with its use is gathered. Suggestions for changes to the MI terms list should be submitted using the appropriate template to the VeDDRA subgroup for consideration at the annual meeting.

All events that occur in humans should be automatically prioritised during signal management process in the Union Pharmacovigilance database.

Further specifications are described here below:

(1) Some VeDDRA PT terms are only considered medically important when associated with a specific species and the related species are specified in the list #.

(2) As a result of the current structure of the VeDDRA list, not all Lower Level Terms (LLT) within a PT term possess the same degree of medical importance and the excluded LLTs terms are specified in the list¤

MI PTs	Species association #	Excluded LLTs ¤
Abdominal pain	Horse	Abdominal cramp, Abdominal discomfort, Praying position, Stomach cramp, Tense abdomen
Abomasitis	Ruminant, Camelid	
Abortion	All	
Acute mastitis	Ruminant, Camelid, Horse	
Aggression	All	
Anaphylaxis	All	
Anorexia	Horse	
Apnoea	All	
Ataxia	Horse	
Bee systemic disorders NOS	Bee	
Birth defect	All	
Blindness	All	
Bone marrow hypoplasia	All	
Cardiac arrest	All	
Cardiac insufficiency	All	
Circulatory shock	All	
Coagulopathy	All	

MI PTs	Species association [#]	Excluded LLTs [¤]
Collapse NOS	All	
Coma	All	
Convulsion	All	
Deafness	All	
Death	All	Unrelated death
Diabetes mellitus	All	
Disseminated intravascular coagulation	All	
Dyspnoea	All	
Epileptic seizure	All	
Fish asphyxia	Fish	
Fish body deformity	Fish	
Haemolytic anaemia	All	
Haemorrhagic gastroenteritis	All	
Heart block	All	
Hepatic failure	All	
Hypersensitivity reaction	All	Allergic pruritus, Allergic reaction, Allergic skin reaction, Allergy NOS
Hypocalcaemic condition	Ruminant, Camelid	
Hypomagnesaemic condition	Ruminant, Camelid	
Impaired hearing	All	
Impaired vision	All	
Immune mediated thrombocytopenia	All	
Increased coagulation time	All	
Ketosis	Ruminant, Camelid	
Laminitis	Horse	
Loss of consciousness	All	
Lying down	Horse, Ruminant, Pig, Camelid	
Metastatic neoplasia	All	
Metritis	Horse, Ruminant, Camelid	
Moribund	All	
Multi-organ failure NOS	All	
Myoglobinuria (Horses only)	Horse	
Paralysis	All	
Paresis	All	
Perinatal mortality	All	
Recumbency	Horse, Ruminant, Pig, Camelid	
Renal insufficiency	All	
Reticulitis	Ruminant, Camelid	
Stillbirth	All	
Suspected infectious agent transmission	All	
Thrombocytopenia	All	

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