18 November 2021
EMA/522332/2020

Guideline on veterinary good pharmacovigilance practices (VGVP)

Module: Signal Management

Endorsed by Coordination group for Mutual recognition and Decentralised procedures (veterinary) (CMDv) for release for consultation	14 May 2021
Draft agreed by Committee for Medicinal Products for Veterinary Use (CVMP) Pharmacovigilance Working Party (PhVWP-V)	26 May 2021
Adopted by CVMP for release for consultation	17 June 2021
Start of public consultation	5 July 2021
End of consultation (deadline for comments)	5 September 2021
Agreed by PhVWP-V	22 September 2021
Adopted by CVMP	4 November 2021
Endorsed by CMDv	5 November 2021
Date for coming into effect	28 January 2022

Keywords	***Veterinary pharmacovigilance; signal management; Regulation (EU) 2019/6; Union pharmacovigilance database***

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of Contents

1. Introduction

This module of the guideline 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).

Article 17(5) of Commission Implementing Regulation (EU) 2021/1281 requires the Agency to publish guidance on best practice for signal management.

The objectives of this module are:

- to provide general guidance 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 veterinary medicinal products authorised in the EU irrespective of the authorisation procedure (centralised or national procedure, including mutual recognition, decentralised and subsequent recognition procedures) and registered homeopathic veterinary medicinal 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.

For the scope of this module, the responsibilities of registration holders of homeopathic veterinary medicinal products are the same as those for marketing authorisation holders.

The guidance in this module will be reviewed and updated in the future based 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) 2021/1281, 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).

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 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 (Article 1(c) of Commission Implementing Regulation (EU) 2021/1281).

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.

In practice, for signals involving spontaneous reports, usually several case reports are needed to trigger a signal. Only in very rare cases would a single well-documented report concerning a serious adverse event or involving several animals be enough to trigger a signal. As a simple rule in the Union pharmacovigilance database, cumulatively over the full life cycle of a veterinary medicinal product, a minimum of 3 case reports is needed for signals concerning Medically Important (MI) VeDDRA terms (see section 2.3.2) or 5 case reports for signals involving any other VeDDRA terms. However, flexibility should always be applied, and this should not be understood as a strict rule.

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, prioritisation, 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, identified by the marketing authorisation holder according to Article 58(10) of Regulation (EU) 2019/6, the marketing authorisation holder should notify it to the relevant competent authority(ies) without delay and no later than 3 working days following their identification (see section 2.3.1).

Where the outcome of the signal management process identifies a change to the benefit-risk balance or a new risk, the marketing authorisation holder shall notify it without delay and no later than 30 calendar days 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.

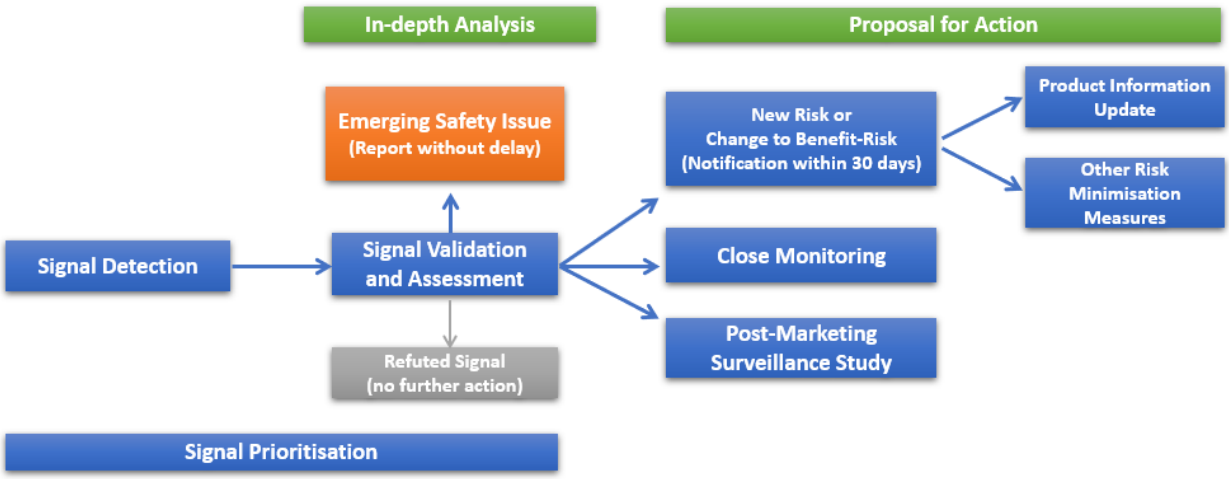

Figure 1. Overview of the signal management process for veterinary medicinal products.

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 of 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, 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 prioritisation should be performed throughout the whole signal management process, from signal detection to 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 are presented in order of importance, with emerging safety issues and signals involving medically important terms 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 veterinary medicinal product 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 working days after its identification. 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 the EU, 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 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 the Agency. This should be done as soon as possible and no later than 3 working 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, 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 the Agency and relevant national competent authorities as soon as it becomes available.

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 consultation with the incident review group, if warranted (see incident management plan for medicines for veterinary use[1]).

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) VeDDRA terms

A list of Medically Important (MI) terms has been developed (Appendix 1) using 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.

Signals involving MI VeDDRA terms should always be prioritised even in the absence of any statistical disproportionality measure (e.g. ROR[2]), unless they are already considered adequately reflected in the current product information.

2.3.3. Prioritisation criteria for other types of signals

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

When prioritising newly identified signals other 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 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.

[1] https://www.ema.europa.eu/en/documents/other/incident-management-plan-medicines-veterinary-use_en.pdf
[2] 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.

- 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 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.

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.

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 products considered the same or similar[3].

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 [4].
- If needed, more tailored queries can be constructed based on the individual data elements.

The outputs of the 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. It is acknowledged that other analytical tools, including other statistical methods that are known to be used in the field of pharmacovigilance, such as Bayesian methods, can be used by marketing authorisation holders in their own databases and can be useful to detect signals. However, all marketing authorisation holders shall conduct at least one signal

[3] VICH GL24 on pharmacovigilance of veterinary medicinal products: management of adverse event reports (AERs).
[4] Incidence calculation queries are expected to become available from 2023 onwards (Article 75, 3(a) of the Regulation EU 2019/6)

detection analysis per year for each of their active substances or products in the Union pharmacovigilance database (Article 17(7) of Commission Implementing Regulation (EU) 2021/1281). This signal detection analysis should be performed within 2 months before the annual due date (see section 3.1).

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 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 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 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 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.).

Signal validation serves thus as a 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 Union pharmacovigilance database.

Once a signal is validated, further assessment shall be performed by the marketing authorisation 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 (see section 3.3).
- 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 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.

2.6. 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 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 minimisation measures and 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 considered, 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).
  - Notify within 30 calendar days with a proposal for the necessary action (Article 81(2) of Regulation (EU) 2019/6) and any risk minimisation measures as applicable.
- The available information suggests that a potential causal association is at present unlikely;
  - Signal refuted, no further action besides routine pharmacovigilance (see section 2.6.1).
- 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 2.6.2).
- A post-marketing surveillance study is required to further investigate the issue (see section 2.6.3).

2.6.1. 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.

2.6.2. 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 authorisation 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.

2.6.3. 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 authorisation 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 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.

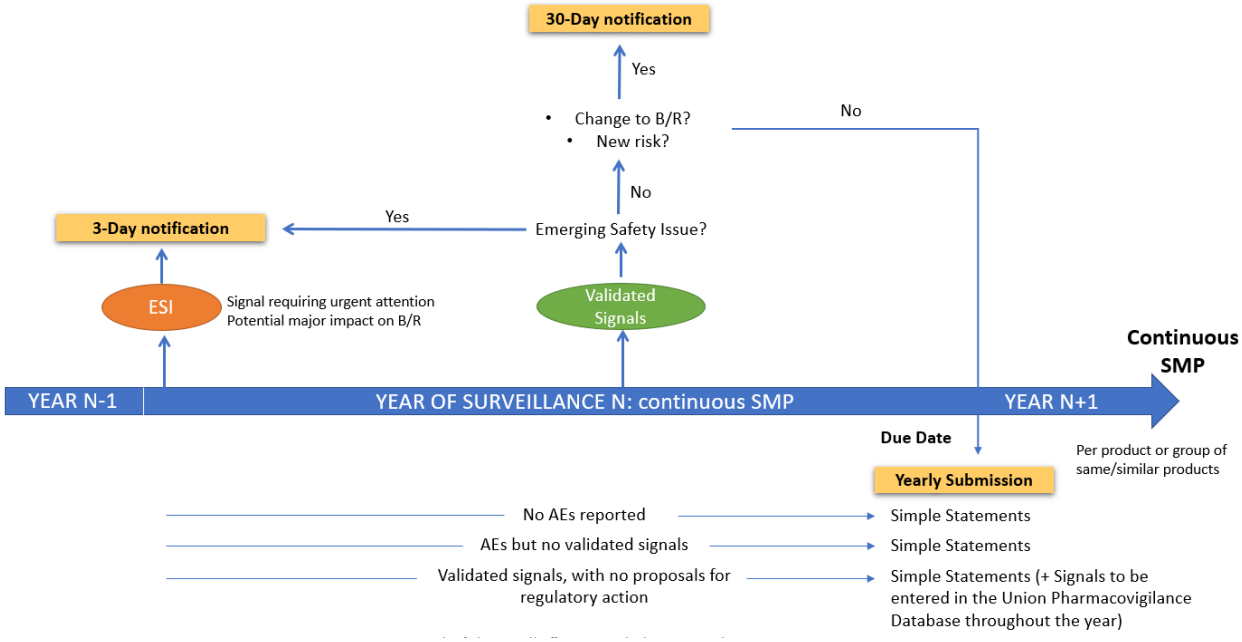

Figure 2. Summary overview of the continuous signal management process performed by marketing authorisation holders throughout a year of surveillance

3.1. Roles, responsibilities, and procedural aspects

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. 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 holders which require further regulatory action (including emerging safety issues and signals where a new risk or a change to the benefit-risk balance is identified) and
- the review of an annual statement by the marketing authorisation holder on the benefit-risk balance of the veterinary medicinal product together with the validated signals assessed throughout the year which did not require urgent attention or did not lead to any proposals for further regulatory action. As part of their annual submission, marketing authorisation holders are required to confirm that the signal management procedure has been conducted and all assessed signals have been submitted.

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) will be set up for all active substances concerned. These will be defined annually, although more frequent submissions may be specified by the Agency (e.g. for specific new active substances (Article 81(2) referring to Article 42(2)(c)).

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), should be notified as soon as possible and no later than 3 working days following their identification 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 new risk or change to the benefit-risk balance, that requires further regulatory action (e.g. updating the product information with a warning), 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.

The data to be entered should include the following fields:

- Administrative information: name of medicinal product(s), marketing authorisation holder, active substance(s).
- For each signal: one entry specifying the species and the VeDDRA Preferred Term(s) or type of adverse event(s), cumulative number of cases and cases supporting the signal (providing the corresponding case numbers). The results of the signal assessment should be presented in an appropriate signal assessment report which should include a conclusion on the potential causal association and proposals for regulatory action, including any risk minimisation measures as necessary.

3.2.2. Annual submission including annual statement

As laid down by Article 81(2) of Regulation (EU) 2019/6 and Article 19 of Commission Implementing Regulation (EU) 2021/1281, at least annually, marketing authorisation holders shall record a conclusion on the benefit-risk balance for 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 whether any signals were detected throughout the year. If no signal was detected or validated, a standard statement confirming that the signal management process has been conducted in line with the guidance in this module and a statement confirming that the benefit-risk balance of the concerned veterinary medicinal product is unchanged will be sufficient.

This obligation applies for each veterinary medicinal product for which the marketing authorisation holder is responsible (but grouping will be allowed on the basis of same or similar products).

The annual submission should take place at the latest by the due date set for each active substance. Signals requiring reporting without delay (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 resubmitted, unless new relevant information has become available. In case new relevant information becomes available, the marketing authorisation holder should consider reopening and reassessing the signal. As always, if there are any changes to the benefit-risk balance or a new risk identified and therefore any proposed regulatory actions, the signal should then be reported without delay (30-day notification requirement).

All validated and assessed signals throughout the year that do not result in proposals for further regulatory action by the marketing authorisation holder (i.e. where the conclusion of the assessment is to refute the signal or propose close monitoring) should be recorded in the Union pharmacovigilance

database by the annual due date, at the latest. These signals can be submitted at any time throughout the year. At the time of submission of the annual statements, the marketing authorisation holder will have to confirm that all assessed signals have been submitted accordingly in the Union pharmacovigilance database.

The data to be entered should include the following fields:

- Administrative information: name of veterinary medicinal product(s), marketing authorisation holder, active substance(s).
- Per signal: one entry specifying the species and the VeDDRA Preferred Term(s) or type of adverse event(s), cumulative number of cases, with a brief summary of the review of the cases and the conclusion on the assessment (either proposing to refute the signal or close monitoring). 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 should be updated by the due date with a summary of the new and similar cases received since the last update.
- For signals under close monitoring for an extended period of time (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.
- Refuted signals from previous annual submissions with no new relevant information available do not need to be resubmitted.

3.3. Incidence reporting by marketing authorisation

As described in Article 75(3) from Regulation (EU) 2019/6, the annual incidence data from suspected adverse events for each veterinary medicinal product by animal species and type of suspected adverse event should be made available for access to the general public in the Union pharmacovigilance database at the latest within two years from 28 January 2022.

3.4. Reporting of other additional information

The signal module of the Union pharmacovigilance database also allows marketing authorisation holders to report additional information as applicable, for example on the following issues:

- scientific literature findings on suspected adverse events concerning a group of humans who cannot be identified individually for recording separate suspected adverse event reports (see section 2.2 from VGVP module on collection and recording of suspected adverse events for veterinary medicinal products),
- risks or relevant issues identified from off-label use cases with no suspected adverse events (see section 2.16 from VGVP module on collection and recording of suspected adverse events for veterinary medicinal products),
- risks or relevant issues identified from "Special situation cases", not based on suspected adverse events (see section 2.17 from VGVP module on collection and recording of suspected adverse events for veterinary medicinal products).

3.5. Targeted signal management by the competent authorities and the Agency

As described in Article 81(3) from Regulation (EU) 2019/6, the competent authorities and the Agency have the option to perform a targeted signal management process for a given veterinary medicinal product or group of veterinary medicinal products.

Regulators can start a signal management procedure at any time throughout the year. Marketing authorisation holders should collaborate with the Agency and national competent authorities in any targeted signal management initiated by the competent authorities and provide any requested information in a timely manner.

3.6. 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 of the Committee for Veterinary Medicinal Products (PhVWP-V), Committee for Veterinary Medicinal Products (CVMP) and Coordination group for mutual recognition and decentralised procedures for veterinary medicinal products (CMDv) agendas.
- CVMP and CMDv recommendations.
- Cumulative list of signals discussed by the CVMP and CMDv with links to the relevant minutes.
- List of due dates for the submission of the annual signal management outcomes and statements 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. These elements should be available for inspection.

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 for relevant definitions.

Appendix 1. Medically Important (MI) VeDDRA terms list

As a guidance to prioritise the analysis of data during signal detection in the Union Pharmacovigilance database, a Medically Important (MI) VeDDRA terms list has been developed. This list should be used by the European Medicines Agency, as well as EEA Member States, and market authorisation holders for signal prioritisation, as described in this module. The MI VeDDRA 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. on calculating if the observed incidence is similar to the expected incidence, etc.).

The content of 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. Preferred 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 additions or amendments to the MI terms list should be submitted to the PhVWP-V for consideration.

- Some VeDDRA PT terms are only considered medically important when associated with a specific species and the related species are specified in the list.
- All events that occur in humans should be automatically prioritised during signal management process in the Union pharmacovigilance database.
- Reports related to lack of expected efficacy (LEE) should also be automatically prioritised, especially for products used for anaesthesia or euthanasia.

MI VeDDRA term	Species #
Any event	Human
Abdominal pain	Horse
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
Collapse NOS*	All
Coma	All
Convulsion	All
Deafness	All

MI VeDDRA term	Species #
Death	All
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
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

*NOS: Not otherwise specified.