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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: Collection and recording of suspected adverse events for veterinary medicinal products

Draft

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Comments should be provided using this template. The completed comments form should be sent to Vet-Guidelines@ema.europa.eu

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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 Agency on the requirements, roles, activities and procedures related to collection and recording of suspected adverse events for veterinary medicinal products occurring within the EU/EEA or in third countries.

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.

Suspected adverse event reporting is the primary information source for post-authorisation 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 when marketed.

Suspected adverse event reports are recorded in the Union pharmacovigilance database (EVV), which is interconnected to the Union product database (UPD).

This module provides details on the principles and procedures for best practice on collection, reporting and recording of suspected adverse events for veterinary medicinal products for marketing authorisation holders, national competent authorities, the Agency and the Commission for safeguarding animal and public health and the environment. This module is applicable to authorised veterinary medicinal products in the EU irrespective of the authorisation procedure (centralised or national authorisation, including mutual recognition, decentralised and subsequent recognition procedures).

This module must 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 <reference to the Commission Implementing Regulation to be completed when available>.

2. Structures and processes

2.1. Collection of suspected adverse events

National competent authorities, the Agency and marketing authorisation holders should encourage the reporting of suspected adverse events associated with authorised veterinary medicinal products originating from unsolicited or solicited sources.

National competent authorities, the Commission, the Agency and marketing authorisation holders shall collaborate in setting up and maintaining a Union pharmacovigilance database to carry out pharmacovigilance tasks with respect to the safety and efficacy of authorised veterinary medicinal products in order to ensure continuous assessment of the benefit-risk balance (see Article 73(1) of Regulation (EU) 2019/6).

National competent authorities and marketing authorisation holders should take appropriate measures to collect and collate all reports of suspected adverse events associated with authorised veterinary medicinal products originating from unsolicited or solicited sources.

The following suspected adverse events shall be collected and recorded in the Union pharmacovigilance database by the marketing authorisation holders and the national competent authorities (see Article 73(2) of Regulation (EU) 2019/6):

- Any unfavourable and unintended reaction in any animal to a veterinary medicinal product;
- Any observation of a lack of efficacy of a veterinary medicinal product following its administration to an animal, whether or not in accordance with the summary of product characteristics;
- Any environmental incidents observed following the administration of a veterinary medicinal product to an animal;
- Any noxious reaction in humans exposed to a veterinary medicinal product;
- Any finding of a pharmacologically active substance or marker residue in a product of animal origin exceeding the maximum levels of residues established in accordance with Regulation (EC) No 470/2009 after the set withdrawal period has been respected;
- Any suspected transmission of an infectious agent via a veterinary medicinal product;
- Any unfavourable and unintended reaction in an animal to a medicinal product for human use.

In accordance with the quality management system requirements as stated in Chapter 2 of the Commission Implementing Regulation and in the VGVP module on Controls and pharmacovigilance Inspections, the marketing authorisation holders should have procedures in place to ensure that the collection of suspected adverse events and their recording in the Union pharmacovigilance database complies with the legislative requirements and the further details provided in this module, as appropriate.

2.1.1. Unsolicited reports

2.1.1.1. Spontaneous reports

A spontaneous report is an unsolicited communication by a veterinarian or other healthcare professional or a member of the general public to a national competent authority, marketing authorisation holder or other organisation (e.g. regional pharmacovigilance centre, poison control centre) 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 organised data collection systems. All spontaneous suspected adverse event reports shall be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from their date of receipt in line with the time frame stated in line with Article 76(1) and (2) of Regulation (EU) 2019/6 (see section 2.2 for validation of suspected adverse event reports).

2.1.1.2. 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 authorisation holders are therefore expected to review scientific literature in line with their internal procedures using relevant databases for information related to their authorised veterinary medicinal products.

Marketing authorisation 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 in the Union pharmacovigilance database prior to the 'Due date' set for the signal management procedure (i.e. the agreed annual date for the marketing authorisation holders to submit the signal management analysis and the annual statements) for each of their authorised veterinary medicinal products.

Marketing authorisation holders shall record in the Union pharmacovigilance database the suspected adverse event reports identified in scientific literature without delay and no later than within 30 days from their date of receipt in line with the time frame stated in Article 76(2) of Regulation (EU) 2019/6, whenever their authorised veterinary medicinal product(s) has/have been identified in the literature records.

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 authorisation holders should ensure that procedures are in place to monitor publications in relevant peer-reviewed scientific journals. In case the marketing authorisation holders become aware of publications in non-peer-reviewed local journals, these publications should be reported as well. Marketing authorisation 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.

Contractual arrangements may be made with a third party (person or organisation) to perform literature searches and record any identified suspected adverse events in the Union pharmacovigilance database. If a third party is performing these tasks, procedures and detailed agreements shall be in place and documented according to Article 21(2) of the Commission Implementing Regulation following the guidance provided in the VGVP module on Controls and pharmacovigilance Inspections to ensure that the marketing authorisation holder is promptly made aware of any suspected adverse events described in the scientific literature. The deadline for recording in the Union pharmacovigilance database of suspected adverse events identified by a third party in the literature should be based upon when the third party becomes aware of a publication containing the minimum information for a valid suspected adverse event report.

2.1.1.3. Reports from non-medical sources, internet or digital media

Marketing authorisation holders are not expected to extensively search the internet or non-medical sources (e.g. lay press) not being under their management or responsibility (e.g. non-company sponsored) for suspected adverse event reports. Marketing authorisation holders should regularly screen the internet or digital media[1] under their management or responsibility, for any reports of suspected adverse events. The frequency of screening should allow for suspected adverse event reports to be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from the date the information was posted on the internet site/digital media, in line with the time frame stated in Article 76(2) of Regulation (EU) 2019/6. Marketing authorisation holders may consider utilising their websites to facilitate the collection of suspected adverse event reports. If a marketing authorisation holder becomes aware of a report of a suspected adverse event described in any non-company sponsored digital medium or non-medical source, reasonable efforts, as described in internal procedures of the marketing authorisation holder, should be made to follow-up the case in order to obtain the minimum information that constitutes a valid suspected adverse event report. All suspected adverse event reports originating from any non-company sponsored digital medium or non-

[1] Although not exhaustive, the following list should be considered as digital media: web site, web page, blog, vlog, social network, internet forum, chat room, health portal.

medical source should be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from the date the marketing authorisation holder was made aware of the report, in line with the time frame stated in Article 76(2) of Regulation (EU) 2019/6. In relation to cases from the internet or digital media, the ability to identify a reporter for a valid suspected adverse event report may depend on verifying the existence of a real person based on the information available e.g. an email address. If the country of the primary source is missing, the country where the information was received should be used as the primary source country.

2.1.2. Solicited reports

All suspected adverse event reports originating from clinical studies for authorised veterinary medicinal products (e.g. clinical studies conducted to investigate a new indication, a new species, new methods of administration or new combinations) and post-marketing surveillance studies related to veterinary medicinal products (refer to VGVP Annex Glossary for the definition of post-marketing surveillance studies) shall be recorded in the Union pharmacovigilance database in line with the requirements stated in Article 76(1) and (2) of Regulation (EU) 2019/6. These cases should be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from the date of the closure of the final study report.

2.2. Validation of suspected adverse event reports

Suspected adverse event reports from veterinarians or other healthcare professionals or the general public may be submitted in writing, by telephone, or electronically (e.g. via online reporting forms) to national competent authorities or marketing authorisation holders, however they cannot be directly recorded by those veterinarians or other healthcare professionals or the general public in the Union pharmacovigilance database.

Only valid suspected adverse event reports qualify for recording in the Union pharmacovigilance database. A suspected adverse event report should be considered valid when it contains at least the minimum information outlined below. Marketing authorisation holders or national competent authorities are expected to exercise due diligence in following-up the report to collect the missing data elements for a valid report and follow-up activities should be documented.

Additional criteria apply to enable recording suspected adverse event reports in the Union pharmacovigilance database and they may be marked as mandatory or non-mandatory fields (for guidance see EVV - Best practice guide and EU VICH adverse event report implementation guide in Appendix). See also supplementary information provided in sections 2.4-2.10 of this module.

It is essential for marketing authorisation holders and national competent authorities to provide as much detail as possible, including all relevant clinical information, in order to facilitate assessment.

Suspected adverse event reports identified from published scientific literature should be screened, reviewed and assessed to ensure the minimum criteria for reporting of suspected adverse events are satisfied (see section 2.1.1.2).

The reference point for deadlines for recording suspected adverse event reports in the Union pharmacovigilance database (Day zero) is the date of receipt of the minimum information for a valid report (Original Receive Date) irrespective of whether the information is received during a weekend or public holiday. The time frame for recording suspected adverse events in the Union pharmacovigilance database is based on calendar days.

a) Minimum information for a suspected adverse event report to be considered valid:

1. An identifiable primary reporter or source (including the country code):

The primary reporter is the person who first reports the suspected adverse event and corresponds to the primary source of information. In case of follow-up information being reported by a person differing from the primary reporter, this should be recorded in the Union Pharmacovigilance database as 'other reporter'.

Whenever possible, the contact details for the primary reporter should be recorded at the local site of the notified organisation (i.e. marketing authorisation holder or national competent authority) to facilitate follow-up activities. However, if the primary reporter does not wish to provide contact information, the suspected adverse event report should still be considered valid as long as the notified organisation is able to confirm the case directly with the reporter. The identifiability of the reporter refers to the possibility of verification of the existence of a real person based on the information available.

For suspected adverse events identified from the internet or digital media without a known reporting source (see section 2.1.1.3.) reasonable efforts should be made to contact the 'notifier' or 'author' to obtain a contactable email address (i.e. an email address under a valid format and not just a digital media nickname) in order for the suspected adverse event report to be considered valid. The 'notifier' should be encouraged to complete a suspected adverse event reporting form (e.g. marketing authorisation holder or national competent authority form), to ensure the suspected adverse event is captured and recorded in the Union pharmacovigilance database.

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'. The minimum information as presented above also applies.

For suspected adverse events identified in scientific literature, the first publication author (or the corresponding author, if designated) should be considered as the source of information and recorded as primary reporter. Details about the co-authors are not required to be documented among the sources of information. The literature references should be recorded in the Union pharmacovigilance database. Additional relevant identifiers including at least a standardised digital object identifier[2] if available should also be recorded. Should further information be required, the authors of the publication should be contacted.

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

Species ('human' is included in the species list) and number of animals affected is the minimum information required for a valid suspected adverse event report. The number (known or estimated) of animals affected should also include indirectly exposed animals, e.g. animals treated during pregnancy or lactation, co-mingled (e.g. licking topical medicinal products), infectious spread.

If a suspected adverse event in animals involves more than one species, a separate suspected adverse event report should be recorded in the Union pharmacovigilance database for each species involved. These reports should then be linked using the appropriate field.

[2] DOI = digital object identifier, standardised
- (ISO 26324, Information and Documentation - Digital Object Identifier System (2012), - Mechanism for, and emphasis on, enabling re-use of other existing identifier schemes, e.g., ISBN; see 'DOI System and Standard Identifier Schemes'.)

If a suspected adverse event involves more than one human, a separate suspected adverse event report should be recorded in the Union pharmacovigilance database for each human involved. These reports should then be linked using the appropriate field.

For environmental incident(s) (refer to VGVP Annex Glossary for the definition) the following information should be recorded instead of animal species and number of animals reacting: the type of information in the suspected adverse event report should be 'Other' and the VeDDRA term 'Environmental adverse event' should be selected.

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 together with their batch number(s), if available.

Where the name of the medicinal product(s) is(are) not included in the initial report, marketing authorisation holders and national competent authorities shall make reasonable efforts to obtain the name or at least part of the trade name of all medicinal product(s) concerned according to Article 12(3) of the Commission Implementing Regulation. Exceptionally, where (a) specific medicinal product(s) cannot be identified, the name(s) of the active substance(s) shall 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.

In case of suspected adverse event(s) in humans, it may be necessary to contact the investigating medical doctor or national poison/toxicology investigation centre in order to clarify details of the event(s). In case of suspected adverse event(s) in animal(s), it may be necessary to contact the investigating veterinarian in order to clarify details of the event(s).

b) Case narrative

The case narrative is very important and should contain all known relevant clinical and related information as provided by the primary reporter (i.e. original verbatim text reported by the primary reporter) even if this information is also recorded using the VeDDRA terminology, including animal or human or environment details, exposure or treatment details, 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). 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. 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.

Where applicable, the information in the case narrative should also be coded in the relevant fields in the Union pharmacovigilance database to facilitate data analysis.

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. Dechallenge information (e.g. any obvious effect of removal of treatment).
8. Rechallenge 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 sequelae.
    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.

Specifically for reports of suspected adverse event(s) in humans, all known relevant information not otherwise reported, including human details (e.g. sex, age or date of birth, occupation (with relevance to exposure), details on how the exposure occurred (e.g. accidental), the degree of exposure (e.g. the volume injected or splashed), details regarding symptoms, medical diagnosis and any other information regarding the suspected and concomitant medicinal products should be included in the case narrative.

Non-coded information shall be recorded in the Union pharmacovigilance database in a language customary in the field of medical science according to Article 13(2) of the Commission Implementing Regulation. The language customary in the field of medical science in the EU/EEA is English. Where the case narratives and textual descriptions of suspected adverse events are reported to the marketing authorisation holders in an official language of the EU/EEA other than English, the marketing authorisation holders should only record in the Union pharmacovigilance database an accurate translation thereof in the English language. Member States may record case narratives in their official language(s) and for those reports, case translations in English should be provided where requested by the Agency or other Member States for the evaluation of potential signals.

For the recording of suspected adverse events originating outside the EU/EEA the English language should be used.

Suspected and concomitant medicinal product(s)/active substance(s) identification

It is important to record the opinion of the primary reporter identifying which of the medicinal product(s)/active substance(s) are considered suspected or concomitant, when available. This information should be recorded in the case narrative using the prefix: ‘Reporter’s opinion on suspected and concomitant medicinal product(s)/active substance(s):’.

If the attending veterinarian’s assessment is available, indicating which products are considered suspected or concomitant, this information should be also recorded in the case narrative. This information is of particular value when performing in-depth analysis for signal detection. The available

field in the VICH (Veterinary International Conference on Harmonization) guideline on pharmacovigilance VICH GL42[3]: 'B.5.1. Attending veterinarian's assessment' can only capture this type of information at report level, without indicating the actual products, and therefore this field can be left blank.

Furthermore, experience has shown that establishing and recording the potential causal association at individual case report level between all observed suspected adverse events and each of the concerned medicinal products by using a coding system, is often inaccurate, prone to bias, variable over time, and that it can cause a considerable administrative burden. With the institution of the signal management process (see VGVP module on Signal management) as the main pharmacovigilance tool, it is no longer considered necessary for the marketing authorisation holders or the national competent authorities to indicate their interpretation on the potential causal association for each of the medicinal products in the suspected adverse event report at individual case report level. The available fields foreseen by the international standards to collect this information (see VICH GL42[3]: 'B.2.1.5. MAH assessment', 'B.2.1.6. RA assessment'), can therefore be left blank. All medicinal product(s)/active substance(s) included in a suspected adverse event report recorded in the Union pharmacovigilance database will be considered suspected during the process of signal management.

2.3. Suspected adverse events following the use of medicinal products for human use

National competent authorities should pro-actively communicate with veterinarians and other healthcare professionals regarding suspected adverse events in animals following the use of medicinal products for human use in order to encourage reporting of such events to the national competent authorities, pursuant to Article 73(2)(g) of Regulation (EU) 2019/6. By collecting this type of information and recording this information in the Union pharmacovigilance database, national competent authorities should alert veterinarians or where necessary the general public in case of safety concerns.

No legal obligations apply to the marketing authorisation holders for medicinal products for human use for the recording in the Union pharmacovigilance database of suspected adverse events in animals following the use of medicinal products for human use. In case of suspected adverse event reports involving both medicinal products for human use and veterinary medicinal products, it is expected that the marketing authorisation holders for the veterinary medicinal product(s) include in the suspected adverse event report adequate information for the medicinal products for human use as for any other concomitant medicinal products.

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 pre-mix, 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] VICH GL42: Pharmacovigilance: data elements for submission of adverse event reports (AERs)

2.5. Investigation of fatal outcome

In the event of a fatal outcome, the cause of death, if available, should be provided and its relationship to the suspected adverse event be commented upon, preferably by the attending veterinarian. Necropsy findings should be provided if such tests were carried out. The nature of the investigation should be described and a summary of any analysis of samples should be provided, if relevant.

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 recorded in the Union pharmacovigilance database.

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 authorisation holder or national competent authority on the suspected adverse event(s) in humans provided in the case narrative.
- Animal and treatment data, e.g. method of administration, administration site, number and species of animals being treated.

2.7. Reports on investigations of the validity of a withdrawal period

In addition to the minimum information required for a valid suspected adverse event report, the following details should be included in suspected adverse event reports on investigation of the validity of a withdrawal period if available:

- The withdrawal period applied.
- Date of detection of the residues.
- The level of residues detected.
- The location of the case (the country of occurrence).
- The analytical method used to determine the nature and concentration of residues.
- Any other information necessary for a detailed evaluation of the case.
- The steps taken by the marketing authorisation holder to investigate the matter.

The type of information in the suspected adverse event report should be 'Other' and the relevant VeDDRA terms should be selected.

2.8. Suspected adverse event reports after suspension, revocation or withdrawal of a marketing authorisation for safety or commercial reasons

Requirements regarding recording suspected adverse events in the Union pharmacovigilance database remain after suspension of the marketing authorisation of a veterinary medicinal product. Where a marketing authorisation is withdrawn or revoked, the former marketing authorisation holder is encouraged to continue to record in the Union pharmacovigilance database suspected adverse events involving the concerned veterinary medicinal product until the end of the shelf-life of the last batch of that product released to the market.

2.9. 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. 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 (immuno-suppressed /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.

Medicinal products should comply with the recommendations provided in the Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products[4].

Information about any suspected transmission of an infectious agent via a veterinary medicinal product shall be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from the date of receipt of the information, in line with the time frame stated in Article 76(1) and (2) of Regulation (EU) 2019/6. The type of information in the suspected adverse event report should be 'Safety Issue' and the relevant VeDDRA terms should be selected.

2.10. 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.

[4] Ref.: EMA/410/01; EMA website: https://www.ema.europa.eu/en/human-regulatory/research-development/advanced-therapies/guidelines-relevant-advanced-therapy-medicinal-products

Suspected adverse event reports involving suspected or confirmed quality defects shall be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from their date of receipt, in line with the time frame stated in Article 76(1) and (2) of Regulation (EU) 2019/6. The relevant VeDDRA terms should be selected in order to indicate that the case relates to a suspected or confirmed quality defect (*Subject to agreement by the VeDDRA sub-group*).

2.11. Handling of duplicate reports

National competent authorities and marketing authorisation holders receive suspected adverse event reports and record them in the Union pharmacovigilance database. Suspected adverse event reports may be submitted to these organisations by more than one source (e.g. member of the general public, veterinarian), or via the same source through more than one channel (e.g. via an online reporting form and via telephone). As a result, the same report may be recorded in the Union pharmacovigilance database by more than one organisation (e.g. all marketing authorisation holders of all veterinary medicinal products involved in a report or a national competent authority and more than one marketing authorisation holders). Thus, any organisation recording a report in the Union pharmacovigilance database should ensure that it contains as much information as possible in order to facilitate the detection and confirmation of duplicates.

When a duplicate has been identified that was recorded in the Union Pharmacovigilance database by the same original sending organisation, only this sending organisation can nullify one of the reports while ensuring that the remaining report contains all information present in the nullified report.

The Union pharmacovigilance database will be developed to have an algorithm that identifies potential duplicates automatically. After identification and confirmation, these reports will be merged into a single new (or merged) suspected adverse event report, known as the 'master report' (see EU VICH adverse event report implementation guide).

The use of standard terminology for coding suspected adverse events by the marketing authorisation holders and the national competent authorities is essential, as the duplicate detection algorithm in the Union pharmacovigilance database relies on fields containing standard terminology to identify possible duplicates. The use of standard terminology serves to minimise the risk of duplicate suspected adverse event reports and the administrative burden associated with their subsequent management.

2.12. Electronic transmission of suspected adverse event reports

Detailed information and guidance are provided in EVV - Best practice guide, the EU VICH adverse event report implementation guide, EudraVigilance Access Policy for Medicines for Veterinary Use and EudraVigilance VET Registration Manual (see Appendix).

2.13. Follow-up of suspected adverse event reports

Marketing authorisation holders should make reasonable efforts to communicate with the primary reporter as necessary to enable investigation of suspected adverse events, including the results of appropriate diagnostic tests. Where considered appropriate, the marketing authorisation holders are encouraged to support the veterinarians with any additional investigations (e.g. autopsy, laboratory results) required.

Where possible, this should be done before recording the suspected adverse event report in the Union pharmacovigilance database (no later than within 30 days from the date of receipt of the report in line with the time frame stated in Article 76(1) and (2) of Regulation (EU) 2019/6), to ensure complete and quality data is recorded.

If investigation of the suspected adverse event is not completed within 30 days, significant new information should be transmitted in a follow-up report, again without delay and not later than within 30 days of receipt of the significant new information.

Suspected adverse event reports should be followed-up to obtain additional information relevant to the case as necessary, and relevant follow-up information should be recorded in the Union pharmacovigilance database. All available information relevant to the evaluation of the suspected adverse event should be provided.

When national competent authorities receive follow-up information, they should also ensure to record this information in the Union pharmacovigilance database.

How to record follow-up suspected adverse event reports in the Union pharmacovigilance database

The mandatory field 'Date of current submission' ('Most recent info date') (see VICH GL42[3], A.4.3.) taken together with the mandatory fields: 'Type of submission', 'Message number', 'Message Sender Identifier', 'Batch Identifier', 'Batch Sender Identifier' and 'Unique Adverse Event Identification Number' provide a mechanism to identify whether the report being transmitted is an initial or a follow-up report, but automated identification of a follow-up is also included in the system. For this reason, these items are considered critical for each transmission.

When recording a follow-up report, the selected term for the field 'Type of submission' should be 'Follow-up'. The 'Date of current submission' ('Most recent info date'), 'Message number' and 'Batch Identifier' should be changed each time follow-up information is transmitted by the sending organisation.

The 'Unique Adverse Event Identification Number' as assigned to the initial report must not be altered during the recording of follow-up reports in the Union pharmacovigilance database.

New information should be clearly identifiable in the case narrative section and provided in structured format in the applicable fields.

The sending organisation should record a follow-up report in the Union pharmacovigilance database when significant new information has been received. Significant new information relates e.g. to new suspected adverse event(s) and any new or updated information on the case that may impact on its interpretation. As an example, situations where there is inclusion or exclusion of a clinical sign(s) from the list of medically important VeDDRA terms should be considered as significant changes and thus be recorded in the Union pharmacovigilance database as follow-up reports.

2.14. Data privacy management

To comply with EU legislation on the protection of individuals with regard to the processing of personal data, the recording of suspected adverse events in the Union pharmacovigilance database should be operated on the principles of anonymised information.

While the detailed information provided by the primary reporter remains available at either the marketing authorisation holder or the national competent authority to which the suspected adverse event report was first sent, this information should be anonymised when recording the report in the Union pharmacovigilance database, both in the data elements fields and in the narrative. To facilitate the identification of duplicates, while maintaining anonymity of the primary reporter(s) in accordance with data protection legislation, the information of the reporter(s) should be replaced by entering only the initials of the first name and last name and the first two digits of the postcode if available. Otherwise, 'withheld' or 'unknown' should be entered in these fields accordingly.

In case of a suspected adverse event report for a human exposed to veterinary medicinal product(s), additional personal data related to health and medical history of the human experiencing a suspected adverse event may be collected, if required for suspected adverse event processing purposes, while maintaining anonymity of the human concerned.

2.15. Suspected adverse event reports data quality management

Marketing authorisation holders and national competent authorities should have a quality management system in place to ensure compliance with necessary quality standards at every stage of the suspected adverse event report management process such as data collection, data transfer, data management, data coding, suspected adverse event report validation, suspected adverse event report evaluation, follow-up of suspected adverse event reports, suspected adverse event report recording in the Union pharmacovigilance database and archiving.

Correct data entry, including the appropriate use of terminology, should be quality controlled, either systematically or by regular random evaluation. Conformity of stored data with initial and follow-up suspected adverse event reports should be verified by quality control procedures, which permit validation against the original data or images thereof. To facilitate this, the source data (e.g. letters, emails, records of telephone calls, which include details of an event) or an image of the source data should be easily accessible at the location of the primary receipt of the information (marketing authorisation holder or national competent authority). The entire process should be monitored by quality assurance audits.

The Union pharmacovigilance database should be based on the highest internationally recognised data quality standards. To achieve these objectives, national competent authorities and marketing authorisation holders should adhere to the concepts of data structuring, coding and submission in line with the EVV - Best Practice Guide and EU VICH adverse event report implementation guide (see Appendix. This is a pre-requisite to maintain a properly functioning Union pharmacovigilance database intended to fully support the protection of public or animal health or of the environment.

Suspected adverse event reports should contain standard terminology according to Article 12(1) of the Commission Implementing Regulation to allow systematic coding and analysis of suspected adverse events. The Union pharmacovigilance database uses VeDDRA terminology for the recording of suspected adverse events and it accepts the use of the last two versions of the document 'Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products' (see Appendix) and of the document 'Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans' (see Appendix). Furthermore, the latest version of the standard lists included in VICH GL30[5] should be used. National competent authorities and marketing authorisation holders should have their internal lists aligned with the lists used in the Union pharmacovigilance database.

Marketing authorisation holders and national competent authorities should ensure that actions related to data quality management are described in corresponding internal procedures. These actions should consider coding practices with reference to appropriate guidelines and internationally agreed standards, training and measures for corrective and preventive actions.

[5] VICH GL30: Pharmacovigilance: Controlled List of Terms

2.15.1. Data quality management of specific suspected adverse event reports

2.15.1.1. Suspected adverse event reports involving more than one species

If more than one species is involved in the same suspected adverse event, separate reports should be recorded in the Union pharmacovigilance database for each species, although it should be indicated that the reports are linked using the appropriate field. This applies when more than one animal species is involved, or when an animal and a human are involved.

2.15.1.2. Suspected adverse event reports for offspring exposed through a parent

There are different scenarios for cases where parent and offspring experience one or more suspected adverse events following the administration of a veterinary medicinal product to a parent (e.g. mother during pregnancy) resulting in potential exposure of the foetus(es) and during lactation.

If the adverse event is related to a treatment either the mother or the father had received, this should be recorded. A short explanation should be included in the dose details and case narrative to indicate which parent was treated.

The treatment start date should be the treatment start date of the parent. It is recommended that the treatment start date as well as the conception date, if available, are recorded in the case narrative.

Information concerning the number of adult animals treated should be included in the case narrative to indicate what proportion of the flock or herd was affected. This is particularly important in cases of suspected lack of efficacy.

For all scenarios below, the number of animals treated should be the parent treated. The number of animals affected or died should include both the number of parent and the (estimated) number of offspring.

The animal details should be recorded as follows:

a) **In case of a suspected adverse event in both parent and offspring:**

   The clinical signs described in the case narrative, to be recorded as VeDDRA terms in the 'Animal signs' section, should include the clinical signs observed in the offspring as well as those observed in the parent.

b) **In case of a suspected adverse event in both parent and offspring and no offspring being born alive (stillborn or abortion):**

   The clinical signs described in the case narrative, to be recorded as VeDDRA terms in the 'Animal signs' section, should be those observed in the parent. With regards to the offspring, 'Stillbirth' or 'Abortion' should be recorded in the 'Animals signs' section and the number of dead offspring should be stated in the case narrative and recorded as number of animals died.

c) **In case of a suspected adverse event in both parent and offspring and offspring being born alive and dead (stillborn):**

   The clinical signs described in the case narrative, to be recorded as VeDDRA terms in the 'Animal signs' section, should be those observed in the parent and the alive offspring. With regards to the dead offspring, 'Stillbirth' should be recorded in the 'Animals signs' section.

d) **In case the offspring is(are) born alive and experience an adverse event (e.g. malformation, during lactation), while the parent is unaffected:**

The clinical signs described in the case narrative, to be recorded as VeDDRA terms in the 'Animal signs' section, should be those observed in the offspring.

e) **In case no offspring being born alive (stillborn or abortion), while the parent is unaffected:**

'Stillbirth' or 'Abortion' should be recorded in the 'Animals signs' section and the number of dead offspring should be stated in the case narrative and recorded as number of animals died.

For scenarios b, c and e above, in the event of e.g. malformations or congenital disorders in the stillborn or aborted offspring, the relevant VeDDRA terms (in this example 'Malformation NOS' or 'Congenital disorders NOS') should also be recorded in the 'Animal signs' section.

2.16. Off-label use

Upon receipt of a suspected adverse event report, it is important to indicate whether the veterinary medicinal product(s) was(were) used outside the terms of the marketing authorisation.

This information is only collected to facilitate the assessment of the safe and efficacious use of the veterinary medicinal products. It is not intended to monitor or inspect veterinary practices. It is important to emphasize that any personal data related to the primary reporter (e.g. the attending veterinarian) should be handled according to data privacy legislation for validation purposes only of the suspected adverse event report.

Off-label use relates to situations where the veterinary medicinal product is used outside the terms of the marketing authorisation. Reports of suspected adverse events arising from off-label use may be obtained:

- on veterinary medicinal products used outside the terms of the marketing authorisation, e.g. use of a product in non-authorised species/indications, use at doses differing from those set out in the authorised product information (e.g. overdose);
- on veterinary medicinal products used outside the terms of the marketing authorisation in the EU/EEA, but in conformity with the provisions of Articles 112-115 of Regulation (EU) 2019/6 (i.e. 'cascade use').

Off-label use cases <u>with suspected adverse events</u>

Where off-label use cases with the occurrence of one or more suspected adverse events are reported to the marketing authorisation holders or the national competent authorities, they shall be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from their date of receipt, in line with the time frame stated in Article 76(1) and (2) of Regulation (EU) 2019/6.

Off-label use cases <u>with no suspected adverse events</u>

Off-label use cases without the occurrence of one or more suspected adverse events, including asymptomatic human exposure, may present a potential risk of suspected adverse events in the future. These reports may provide valuable information, potentially influencing the evaluation of the benefit-risk balance of the concerned veterinary medicinal product(s). The evaluation of these reports may be useful for the signal management process (see Article 81(1) of Regulation (EU) 2019/6) and may lead to improvements in the product information. Marketing authorisation holders and national competent authorities are advised to keep a record of such cases at their local site but <u>not</u> to record these cases in the Union Pharmacovigilance database. Where such cases are reported to marketing authorisation holders and may have safety implications with a potential impact on the benefit-risk

balance of the concerned veterinary medicinal product(s), the marketing authorisation holders should include them for discussion in the annual statement of the signal management process outcome. In addition, where such cases are reported to national competent authorities and may have safety implications with a potential impact on the benefit-risk balance of the concerned veterinary medicinal product(s), national competent authorities are advised to investigate these cases and take any appropriate actions (e.g. inform the concerned marketing authorisation holder(s), submit a 'Non-Urgent Information' notification to the other Member States).

2.17. Special situations

The terms on special situations listed below (medication error, misuse, abuse and accidental exposure) are to be used only in conjunction with their definition and not necessarily to be applied to every off-label use case.

To facilitate the identification of the special situation cases during the signal management process, several VeDDRA terms have been proposed (*Subject to agreement by the VeDDRA sub-group*).

Medication error

Medication error relates to situations of unintended failure in the veterinary medicinal product treatment process that leads to, or has the potential to lead to, harm to animals or humans, caused by human or process mediated failures, e.g. mistakes in the prescribing, dispensing, storing, preparation and administration of a medicine.

Misuse

Misuse relates to situations of intentional improper or incorrect use of a substance, in both animals and humans, for a purpose not consistent with legal or medical guidelines and outside the provisions of Articles 112-115 of Regulation (EU) 2019/6 ('cascade use'), i.e. the non-medical use of prescription medications.

Abuse

Abuse relates to situations of persistent or sporadic, intentional excessive use of a veterinary medicinal product in animals or humans, which is accompanied by physical or psychological effects.

Accidental exposure

Accidental exposure relates to situations of unintended exposure of an animal or a human to a medicinal product e.g. accidental ingestion. Accidental exposure may also refer to acute, sudden exposure to a medicinal product in the context of an accident which could also be the result of a medication error depending on the circumstances (see also section 2.18).

Special situation cases <u>with suspected adverse events</u>

Where special situation cases with the occurrence of one or more suspected adverse events are reported to the marketing authorisation holders or the national competent authorities, they shall be recorded in the Union pharmacovigilance database without delay and no later than within 30 days from their date of receipt, in line with the time frame stated in Article 76(1) and (2) of Regulation (EU) 2019/6. The relevant VeDDRA term(s) for the adverse event(s) should be selected and also the VeDDRA term(s) for the special situation(s) should be selected accordingly (*Subject to agreement by the VeDDRA sub-group*).

Special situation cases with no suspected adverse events

Special situation cases without the occurrence of one or more suspected adverse events, including asymptomatic human exposure, may present a potential risk of suspected adverse events in the future. These reports may provide valuable information, potentially influencing the evaluation of the benefit-risk balance of the concerned veterinary medicinal product(s). The evaluation of these reports may be useful for the signal management process (see Article 81(1) of Regulation (EU) 2019/6) and may lead to improvements in the product information. Marketing authorisation holders and national competent authorities are advised to keep a record of such cases at their local site but not to record these cases in the Union Pharmacovigilance database. Where such cases are reported to marketing authorisation holders and may have safety implications with a potential impact on the benefit-risk balance of the concerned veterinary medicinal product(s), the marketing authorisation holders should include them for discussion in the annual statement of the signal management process outcome. In addition, where such cases are reported to national competent authorities and may have safety implications with a potential impact on the benefit-risk balance of the concerned veterinary medicinal product(s), national competent authorities are advised to investigate these cases and take any appropriate actions (e.g. inform the concerned marketing authorisation holder(s), submit a 'Non-Urgent Information' notification to the other Member States).

Further guidance is provided in the EVVet - Best practice guide (see Appendix) and the 'Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans' (see Appendix) (*Subject to agreement by the VeDDRA sub-group.*).

2.18. Suspected adverse events involving an untreated animal exposed to a veterinary medicinal product via a treated animal

In case a suspected adverse event has occurred in an untreated animal exposed to a treated animal, even if of different species, a single report should be recorded in the Union pharmacovigilance database relating only to the animal which experienced the suspected adverse event. Where applicable, the VeDDRA term 'Accidental exposure' should be selected *(Subject to agreement by the VeDDRA sub-group)* and a short explanation should be included in the dose details and the case narrative to clearly indicate which animal (or animal species) was treated. In addition, the administration route details should reflect the route by which the affected animal was exposed, e.g. oral route if the contact was by licking or grooming, cutaneous route if there was dermal contact between the treated and untreated animal.

2.19. Suspected adverse event reports related to homeopathic veterinary medicinal products

'Homeopathic veterinary medicinal product' means a veterinary medicinal product prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the European Pharmacopoeia or, in the absence thereof, by the pharmacopoeias used officially in Member States.

Suspected adverse event reports related to homeopathic veterinary medicinal products shall be recorded in the Union pharmacovigilance database within the same time frame as for all suspected adverse event reports.

Definitions

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

Appendix

- EVV - Best practice guide *(Under development)*;
- EU VICH adverse event report implementation guide *(Under public consultation)*;
- EudraVigilance Access Policy for Medicines for Veterinary Use
  https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation/pharmacovigilance/eudravigilance-veterinary#release-of-data-section
- EudraVigilance VET Registration Manual
  https://eudravigilance.ema.europa.eu/veterinary/register.html
- VeDDRA related documents:

  https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation/pharmacovigilance/eudravigilance-veterinary

  - Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products
  - Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans