EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

# Veterinary Union Pharmacovigilance Database – Best Practice Guide

## Contents




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# Introduction

This document has replaced the previous EudraVigilance Veterinary – Best Practice Guide and has been renamed the Veterinary Union Pharmacovigilance Database – Best Practice Guide. The guide has been expanded to accommodate additional guidance and practical advice to facilitate the implementation of three guidelines on veterinary good pharmacovigilance practices (VGVP) as a result of the Regulation 2019/6 entering into force 28 January 2022. The three VGVP Modules that are covered are:

1. Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Collection and recording of suspected adverse events for veterinary medicinal product (europa.eu)
2. Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Signal Management (europa.eu)
3. Guideline on Veterinary Good Pharmacovigilance Practices (VGVP) Module: Controls and pharmacovigilance Inspections

The aim is to provide Market Authorisation Holders (MAHs) and National Competent Authorities (NCAs) with additional practical advice and examples to facilitate the interpretation and implementation of these specific VGVPs. The practical guidance provided covers the use of the main digital systems within the concept of the Union Pharmacovigilance Database, namely EVWeb, Data Warehouse (EVV-DWH) and IRIS. In accordance with the Regulation EU 2019/6, article 73(2) and 74(1), the Agency in collaboration with the Member States, shall establish and maintain a Union Pharmacovigilance Database for reporting and recording of suspected adverse events. EudraVigilance Veterinary (EVV) allows the recording, sending and receiving of adverse event reports (AERs) either via the web user interface (EVWeb) or gateway. EVV-DWH is a query tool to access EVV data such as AERs for detection, analysis and evaluation of signals. IRIS is used for submission of signal management- and inspection outcomes.

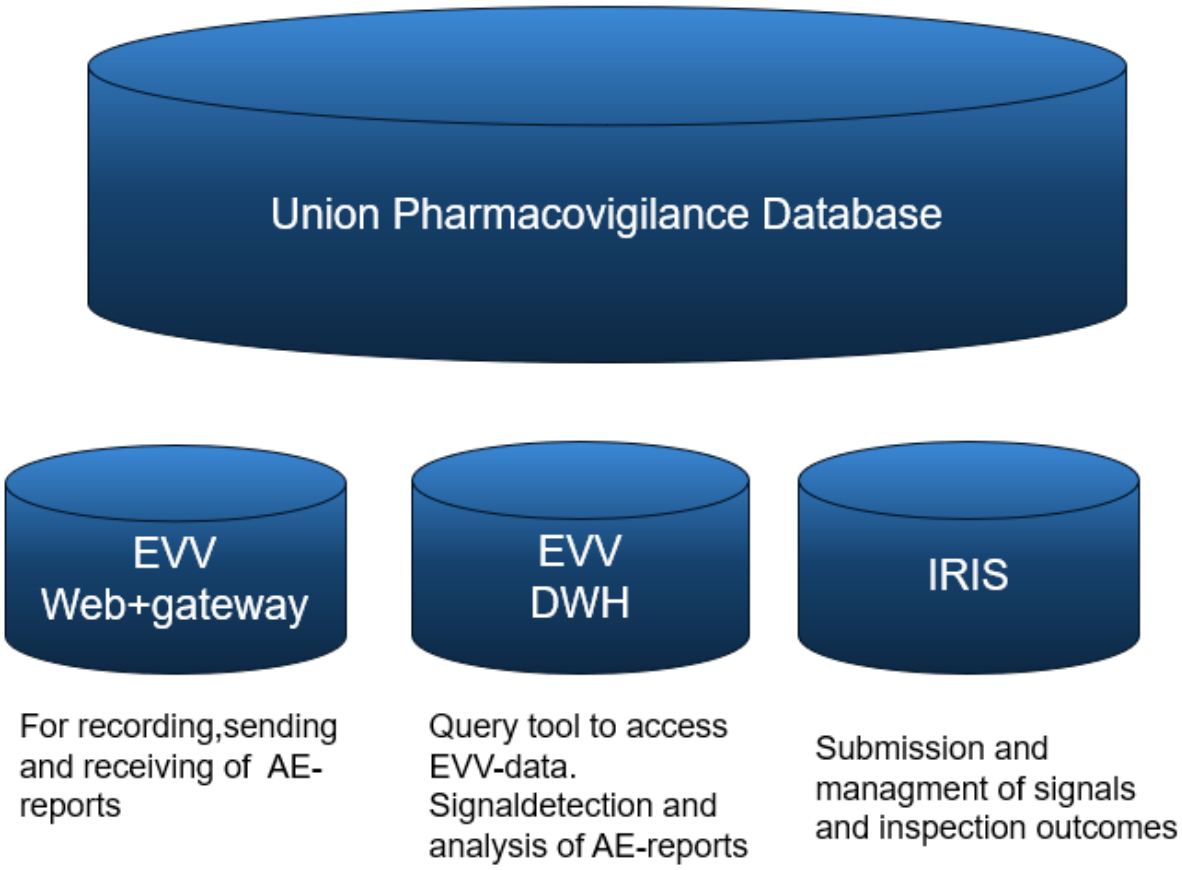



*Illustration of the main digital systems within the concept of the Union Pharmacovigilance Database.*

This document will be updated as experience is gained.

# 1. Chapter - Practical guidance for VGVP Module: Collection and recording of suspected adverse events for veterinary medicinal products.

This document provides guidance to all registered user organisations and their individual users (EVWEB and Gateway users) that record suspected adverse event reports (AERs) in the Union pharmacovigilance database, EudraVigilance Veterinary (EVV).

When recording suspected AERs in EVV, it is important to complete as many of the fields as precisely as possible. The document highlights certain fields or sections which are particularly important for the recording of suspected AERs in EVV. In part the advice is directed to organisations that first record cases in EVV, hereafter called sender organisation. It does not provide a detailed technical description of each of the fields to be completed, which can be found in the guidance documents as follows: EVVET-EVWEB User Manual, EU VICH adverse event report implementation guide, Guidance veterinary International Conference on Harmonisation (VICH), VICH GL42 Pharmacovigilance: data elements for submission of adverse event reports (AERs), VICH GL30 Pharmacovigilance: Controlled List of Terms, VICH GL35 Pharmacovigilance: electronic standards for transfer of data.

Gateway users should take special care to ensure correct transmission of data to EVV. All local databases should be fully VICH compliant which includes having all VICH fields, and not only the mandatory ones. When importing reports from EVV to local databases, the data should not be altered. Mapping or system issues that prevent correct and complete import of reports from EVV to local databases or transmission of correct and complete data from local databases to EVV should be rectified immediately. It should be noted that the correct implementation of VICH standards in local databases may be checked during inspections. Some common examples where information is not correctly transferred to EVV include missing information on linked cases, species or breed codes that are not in compliance with the controlled terms list of the current VICH GL30 or the inability to record cases where the number of treated animals is smaller than the number of affected animals (see also section 1.2.7.).

## *1.1. Administrative and identification information*

### 1.1.1. "Unique Adverse Event Report Identification Number" (AERID)

It is extremely important to provide the "Unique Adverse Event Report Identification Number" (A.4.1) (AERID) in the correct structured format to avoid rejections and to prevent the recording of duplicate AERs (see section 1.3).

The AERID is assigned by the sender organisation that first reports an AER to EVV, and it must never be changed in any subsequent follow-up reports.

- **Regulatory authorities (RA) AERIDs should follow the format below:**

**Country of occurrence code (3 digits)–VICH RA Identifier code (8 digits)–Unique number**

The **Country of occurrence code** is the country where the suspected adverse event (AE) occurred, using the 3-digit country code convention as per VICH guidance (VICH GL30, ISO 3166 International Standard, https://www.iso.org/obp/ui/#search: "Country codes" should be selected and then "search" should be clicked to obtain the 3-digit country code list).

Note:

- "Country of occurrence" of the AER is only stated in the AERID as described above. No separate field is available on the AE reporting form in VICH format, as used by EVV, to provide this information.

- Regulatory Authority (RA) = National Competent Authority (NCA) in the EU Member State that first reports the AER into EVV.

**VICH RA Identifier code:** A unique abbreviation or code for the Regulatory Authority provided in the VICH guideline on pharmacovigilance GL30 "Vocabulary Lists" (see below): Guidelines | vichsec

| VICH RA Identifier Code | RA Name |
|---|---|
| CZEUSKVB | Uskvbl |
| DNKMEDAG | Danish Medicines Agency |
| ESTSAMVP | State Agency Of Medicines |
| FINAMVET | National Agency For Medicines |

**Internal case reference code**: A number given to the case by the organisation sending the AER.

*Example for Danish Agency:*

DNK–DNKMEDAG-12345678

- **The Marketing Authorisation Holder (MAH) AERID should follow the format below:**

**Country of occurrence code (3 digits)-MAHORGID (8 digits** for VICH MAH Identifier code**)-Unique number (ROUTINGID + remaining text (up to 47 digits))**

The **Country of occurrence code** follows the same rule as for the RAs.

**MAHORGID** (VICH MAH Identifier code): MAHs formerly registered in EVVET2, with an existing Routing(sender) ID that is longer or shorter than 8 digits (and have not yet been provided an 8-digit MAHORGID by a different region), will not be able to use it as their MAHORGID, and will need to generate a unique 8-digit MAHORGID from their Routing(sender) ID.

The use of an algorithm (CRC32 Hash Generator) is advised. Various tools are available online. When generating the MAHORGID from the ROUTING(sender) ID, it is advised to enter the ROUTING(sender) ID in capital letters (CAPs). The MAHORGID and the ROUTING(sender) ID obtained should be used for all AERs.

**Unique number**: For MAHs it is advised to include the MAH's ROUTINGID as part of the 'Unique number' to avoid different MAHs generating the same AERID by mistake. The inclusion of the ROUTINGID is not mandated by VICH guidelines, however it is strongly recommended.

**ROUTINGID** = The ID assigned to the organisation when registering with EVV to be used as the "Sender" ID when generating AER messages.

*Example:*

For a MAH with the existing ROUTING(sender) ID "ROUTINGID", following the use of the algorithm to generate the MAHORGID, the AERID for an event that occurred in Germany is as follows:

**DEU-A715DE58-ROUTINGIDxxxxx**

**Important note: When recording follow-up AERs using EVWEB, the AERID for the initial AER becomes non-editable.**

For follow-ups to AERs previously recorded in DEG format and sent before 28/01/2022, please see below:

a) It will be allowed for a limited time for the AERID not to fully comply with the VICH format,

b) The only requirement will be that the AERID needs to contain the 2 or 3 letters country code of the country of occurrence at the beginning of the DEG ID.

**AERs which do not conform with the above-mentioned rules should be nullified. A new AER that follows the correct format should be created instead.**

### 1.1.2. "Original receive date", "Date of current submission" ("Most recent info date") and "Type of submission"

**"Original receive date"**: The date of receipt of the minimum information for a valid AER by an RA/NCA or an MAH, including a third party (person or organisation) with which the MAH has a contractual arrangement, irrespective of whether the information is received during a weekend or public holiday. The time frame for recording suspected adverse events (AEs) in EVV is based on calendar days. **The original receive date is fixed and it cannot be changed when recording follow-up reports.**

**"Date of current submission" ("Most recent info date")**: This is the date when the AER is recorded in EVV.

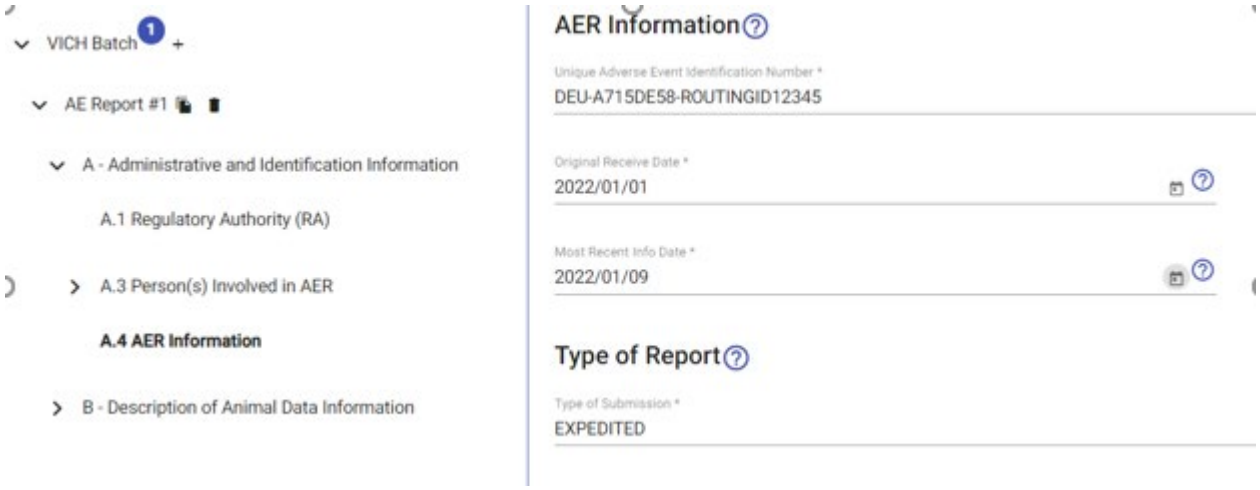
The mandatory field "Date of current submission" ("Most recent info date") (see VICH GL42, A.4.3.) field, taken together with the mandatory fields: "Type of submission" and "Unique Adverse Event Report Identification Number" provides a mechanism to identify whether the report being transmitted is an initial or a follow-up report. For this reason, the entries in these fields are considered critical for each transmission.

*Example:*

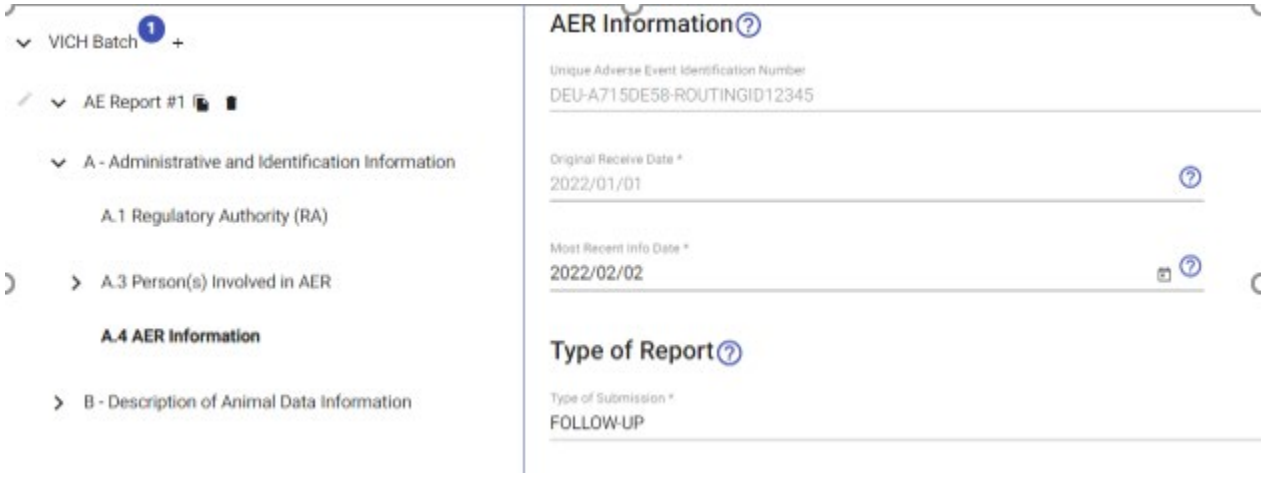
An AER has been recorded by a MAH in EVV concerning an AE that occurred in Germany. The MAH has populated the "Unique Adverse Event Report Identification Number" field as: "DEU-A715DE58-ROUTINGID12345" and the "Type of submission" field as: "Expedited".

If the MAH records a follow-up for the above-mentioned AER in EVV, the MAH should change the "Type of submission" to "Follow-up", however the value of the "Unique Adverse Event Report Identification Number" field should not change, and it should remain as "DEU-A715DE58-ROUTINGID12345".

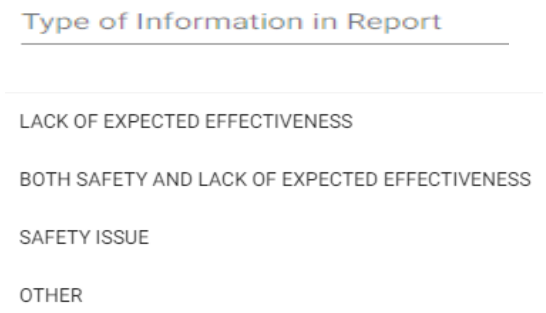
**Initial AER from MAH:**




**Follow-up AER from MAH:**




**"Type of Information in Report"**: This field is to select what type of AER is being recorded in EVV. "Lack of expected effectiveness" (LEE) should be selected for AERs with no safety elements. For AERs with both safety and lack of expected effectiveness elements, "Both safety and lack of expected effectiveness", the relevant VeDDRA term(s) for the AE sign(s) and the VeDDRA term "Lack of efficacy", SHOULD ALL be selected (see also section 1.2.3). For environmental incidents, the value "Other" should be selected (see also section 1.1.3).




The value "Other" should be selected for AERs concerning withdrawal period issues and the relevant VeDDRA term should be recorded.

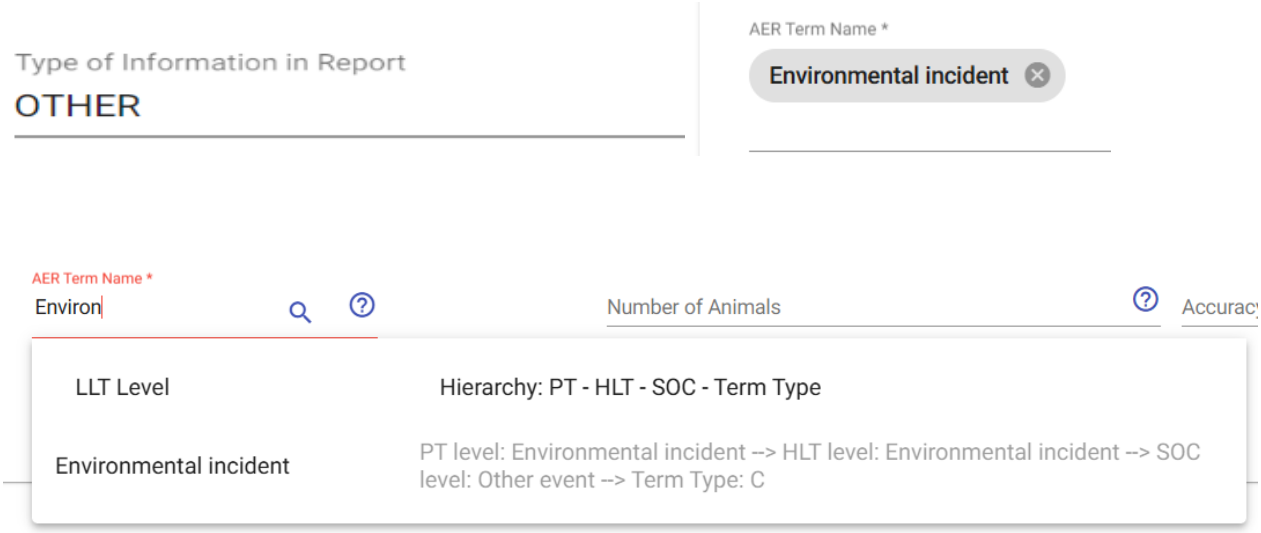
With regards to AERs related to "transmission of infectious agents", the value "Safety issue" should be selected and the relevant VeDDRA term should be recorded.

### 1.1.3. Environmental incidents

For environmental incident(s) (refer to VGVP Glossary for the definition) the following information should be recorded in addition to the animal species and number of animals affected:

- Type of information in the suspected AER should be "Other" in field (A.4.4.3) (see also section 1.1.2),
- The term 'Environmental incident' (SOC Other event, HLT/PT/ LLT Environmental incident) and then relevant VeDDRA term(s) should be selected. Any specific information regarding environmental incidents (e.g. location, nature of environmental incident) should be recorded in the case narrative,
- The route of exposure (e.g. oral, cutaneous) should be selected in the field "Route of Exposure" (B.2.1.7).

*Example from EVV:*

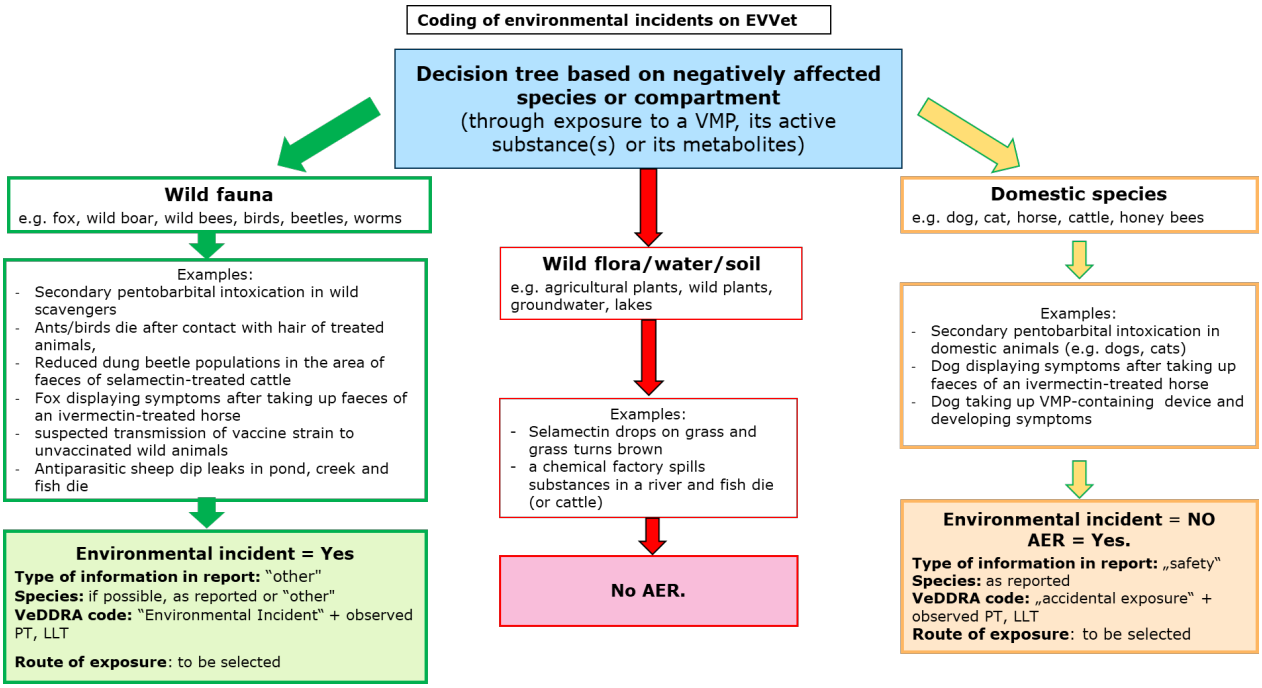



The supporting decision tree graphic has been included as an example for environmental adverse events and to facilitate the coding of such events to EVV. The purpose of this decision tree is to provide additional guidance and clarity on environmental incidents in order to achieve a retrievable dataset in the database enabling structured data analyses. The decision tree will not capture all such potential adverse events as this is an area that is still evolving and should only be taken under consideration as general guidance. As with all adverse events, clinical judgement should be applied on a case-by-case basis.

Generally, an environmental incident affects a wild animal species, such as foxes, wild bees, fish, or birds living in the wild.

As stated in the VGVP Glossary in the definition for environmental incidents, any AER in an animal after taking up animal remains and exhibiting symptoms is to be considered an environmental incident.

With regards to AERs related to "suspected infectious agents transmission, suspected reversal to virulence, suspected transmission of a vaccine strain, suspected recombination of a vaccine strain and suspected prolonged shedding of a vaccine strain", please refer to the VeDDRA guidance notes on the correct use of VeDDRA terminology.




*Example for an environmental AER:*

*Case narrative:*

On DD/MM/YYYY a sheep owner dipped his sheep in a 5,000 litre dip with Product X. The dip was prepared in an old fish pond. This fish pond was not leakproof and an unknown amount of Product X leaked into a river nearby by mistake. Nothing is known about the concentration of the dip. The river meets a small brook and an unknown number of fish (lamprey, moray, trout) died around the estuary. The MAH discussed the issue with the local competent authority for environmental issues and it was decided to suspend the consumption of fish of the affected river for six weeks and corrective measures would be taken by the competent authority.

*Recording in EVV:*

The number of ***affected*** animals recorded in EVV should be the number of fish (**mandatory**).

The species recorded in EVV should be fish (i.e. Affected species).

The VeDDRA terms: "Environmental adverse event" and "Death" should be recorded, including the relevant number of affected animals against each VeDDRA term. If the actual number of the affected animals is not known, an estimated number may be recorded.

Note: The number of treated animals recorded in EVV should be the number of sheep (not mandatory).

## 1.1.4. Primary reporter information

To facilitate the identification of duplicates while maintaining anonymity of the primary reporter(s) in accordance with data protection legislation, the information of the primary reporter(s) should be entered as the initials of the first name and last name and if available, the first two digits of the postcode. This information should be entered as a single entry in the field A.3.1.2 "Primary Reporter Last Name". In case the information is not available, "withheld" or "unknown" should be entered.

The information entered in the "Primary Reporter Information" section of EVV by the initial sender organisation should never be changed when recording a follow-up AER in EVV. In case of additional

information being reported by a person differing from the primary reporter, the anonymised details of this person should be recorded in EVV in the section "other reporter" (A.3.2).

**Primary reporter information:**


### 1.1.5. Personal data

In accordance with the Regulation (EU) 2016/679 (General Data Protection Regulation), information that could lead to the identification of an animal owner, veterinarian or any other person should **not** be included in data element fields or in the case narratives. AERs should be fully anonymised before they are recorded in the Union pharmacovigilance database (see also section 2.14. of the VGVP module on collection and recording of suspected adverse events for veterinary medicinal products).

Examples of personal data that should **NOT** be stated in any data element fields nor in the case narratives:

- names of animals and/or animal owners
- names of veterinary professionals
- names of/ reference to animal hospitals/ treatment centres
- name of laboratory investigators

When personal data is detected in an AER in EVV, the information should be removed without delay and the sender organisation should review their internal standard operating procedure related to data entry. Any changes should be briefly noted at the end of the case narrative as stated in section 1.5 of this document.

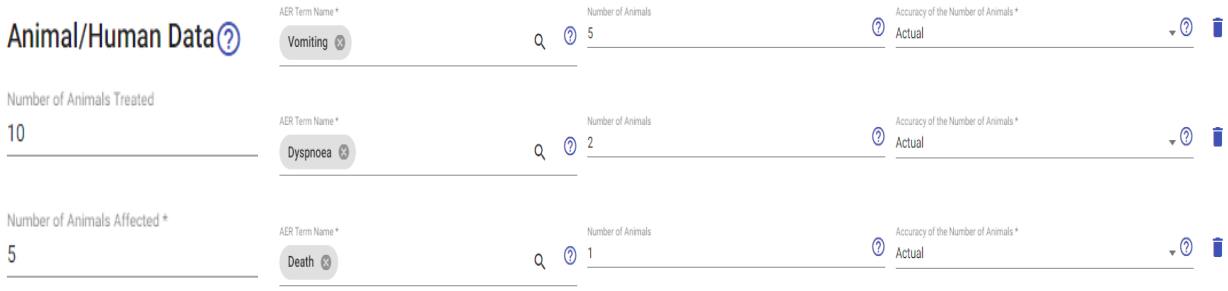
## *1.2. Description of the AE*

### 1.2.1. How to record animal/human data

- **Number of animals/humans treated - Number of animals/humans affected**

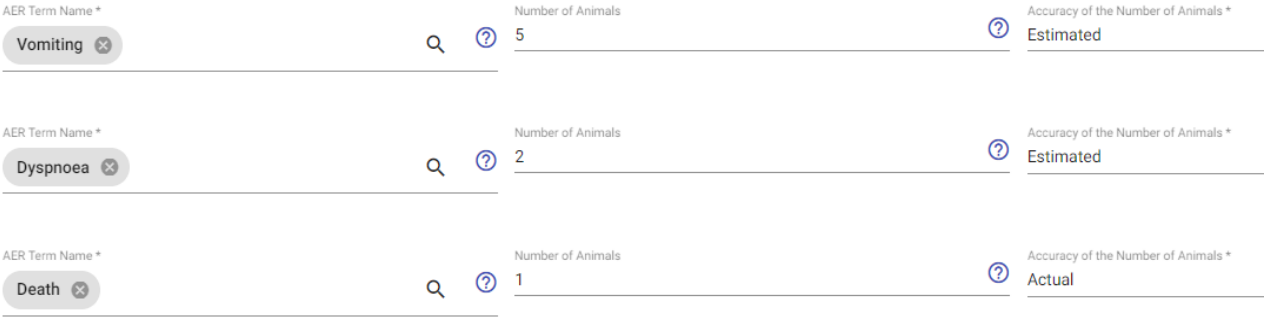
Enter the numbers of animals treated and the number of animals or humans exposed and affected (it is possible to record a higher number of animals affected than treated if applicable). For AERs related to humans, record the actual number of human(s) exposed (if unknown => use 1) but the number affected is always **one** human per suspected AER. If a suspected AE involves more than one human, separate AERs should be recorded in EVV for each human involved. These AERs should then be linked using the appropriate field in the linked report section (B.6). The "Unique Adverse Event Report Identification Number" for any other reports which are related to this AER can be entered in B.6.1 and the explanation for the linkage should be entered in B.6.1.1 as "Similar reports from same reporter (cluster)" or "Other link type" according to what is considered most appropriate for the case. If the actual number of humans affected is not known, only one AER should be recorded, indicating the fact in the narrative that the actual number of affected humans is not known.

**Number of animals treated/affected:**




If the number of animals treated is not known, the estimated number of treated animals should be provided.

If the number of animals affected is not known, the estimated number of affected animals should be provided.




In some cases, it is preferable to express the data for the "Number of animals treated" (B.1.1) and "Number of animals affected" (B.1.2) as a group. For example, for honeybees the number of beehives should be reported instead of the number of single bees. The fact that the number of beehives and not the number of bees has been reported should be indicated in the case narrative.

Please note that if fatal outcomes are reported, the number of dead animals or humans should also be recorded in the relevant fields ("Outcome to date", B.3.8) in the "Adverse event data" section (B.3).

When the VeDDRA term "Death" or "Death by euthanasia" has been included in the AER, the number (known or estimated) of animals or humans should be recorded against each VeDDRA term.

- **Species and Breed (affected)**

For AERs involving a single purebred animal (B.1.4.1), the breed should be entered in B.1.4.1.1 "Breed (purebred)".

For AERs involving a single crossbred animal (B.1.4.2) where the breeds in the cross are known, up to 3 breeds can be listed in B.1.4.2.1 "Breed (crossbred)". If the breed makeup of this single crossbred animal is unknown, use the term "Crossbred ("Species")" and the relevant code in B.1.4.2.1. For example, use term "Crossbred Canine/dog" and code "DOG88", or term "Crossbred Feline/cat" and code "CAT21", etc.

For groups of purebred animals, list the breeds of the affected animals in B.1.4.1.1 "Breed (purebred)".

For groups of both purebred and crossbred affected animals B.1.4.1.1 and B.1.4.2.1 should be populated respectively. When affected animals include various crossbreds and their breed makeup is known, use B.1.4.2.1 as a repeatable field to capture each breed.

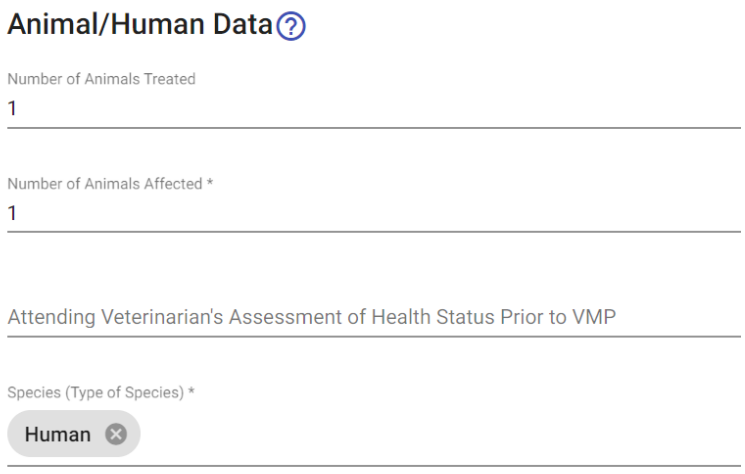
When affected animals include various crossbreeds and the breed makeup of some of the crossbreds is unknown, then also include the term "Crossbred ("Species")" and the relevant code in B.1.4.2.1, e.g. term "Crossbred Canine/dog" and code "DOG88", term "Crossbred Feline/cat" and code "CAT21", etc. The breeds of treated but not affected animals may be entered in the case narrative, if relevant.

For AERs where the breed is either unknown or does not exist in the VICH breed list currently implemented in EVV, the correct practice in these cases (using "dog" as an example) is to use, for example, the species code "DOG"; if the breed is unknown the breed term "Dog (Unknown)" (code "DOG102") should be selected. If the breed is known but the breed name is not included in the VICH breed list, the breed term "Dog (Other)" (code "DOG208") should be selected and the breed name should be added in the case narrative.

If the AER concerns a species that is not included in the VICH species list, the term "Other" should be selected (code "C17649").

If a suspected AE in animals involves more than one species, a separate AER should be recorded in the EVV for each species involved. These AERs should then be linked using the appropriate field in the linked report section in EVV, "B.6" "Report Number(s) of Linked Report(s)". The "Unique Adverse Event Report Identification Number" for any other AERs related to this suspected AE can be entered in "B.6.1" "Unique Adverse Event Report Identification Number". The explanation for the linkage should be entered in "B.6.1.1" "Explanation for Linkage" as "Similar reports from same reporter (cluster)" or "Other link type" according to what is considered most appropriate for the case.

To record an AER in humans, the species "Human" ("HUM") should be selected. Each AER should concern only one human.




- **Gender**

If gender is recorded for one animal, field B.1.5 should be completed with "Male", "Female". If the gender is unknown, the value "Unknown" can be selected in the field B.1.5.

For groups of animals, the value "Mixed" should be selected if both males and females are involved.

- **Weight**

If weight is recorded, field B.1.8.1 should be completed with "Measured" or "Estimated". If the weight is unknown, the value "Unknown" should be selected in field B.1.8.1, and the minimum and maximum weight should not be recorded.

For one animal: Provide weight (kg) in the minimum weight field (B.1.8.2).

For groups of animals: Provide weight (kg) in the minimum weight field (B.1.8.2) and the maximum weight field (B.1.8.3).

- **Age**

If age is recorded, field B.1.9.1 should be completed with "Measured" or "Estimated". If the age is unknown, the value "Unknown" should be selected in field B.1.9.1, and the minimum and maximum age should not be recorded.

For one animal: Provide age in the minimum age field (B.1.9.2). The minimum age units of the animal affected should be recorded in field B.1.9.2.1.

For groups of animals: Provide age in the minimum age field (B.1.9.2) and the maximum age field (B.1.9.3). The maximum age units of the animal affected should be recorded in the field B.1.9.3.1.

### 1.2.2. How to record VMP(s) data and usage

In accordance with the VGVP module on collection and recording of suspected AEs for VMPs, all medicinal products mentioned in the AER must be recorded in the relevant VICH data fields.

The correct recording of the medicinal product name on the "Registered Name" or "Brand name" (B.2.1) and the Authorisation Number in the Registration Identifier (B.2.1.2) fields is very important for subsequent data analysis.

Only medicinal products that have the status of veterinary medicinal products or medicinal products for human use should be recorded in this section.

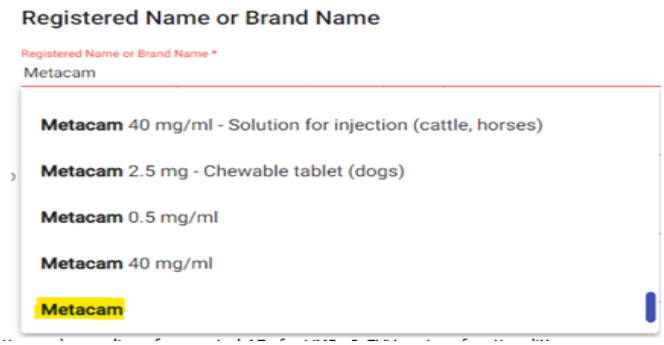
The Union Product Database (UPD) is the source of this information in EVV for veterinary medicinal products. Information related to non-medicinal products (e.g. food supplements, biocides) should only be included in the case narrative.

When recording the product name of a **veterinary medicinal product**, the full name including strength and dosage form should be recorded, if known. EVWEB users should select an entry marked with the symbol  . This will ensure that the veterinary medicinal product mentioned in the AER is automatically linked with the UPD, which is crucial for allowing L2 access to the case (L2 access to AERs for MAH products recorded in EVV by other organisations allows access to case narrative, and also enables grouping of products for signal detection; see also the Access policy for EVV: https://www.ema.europa.eu/en/documents/scientific-guideline/eudravigilance-access-policy-medicines-veterinary-use-revision-2_en.pdf).

*Example from EVV:*


If the **precise full** registered or brand name of the veterinary medicinal product is not known, it is recommended to enter in this field as much information as it is available, e.g. "Invented name".

*Example from EVV:*



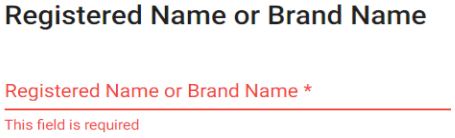

In some instances, when non-specific product information has been received from the primary reporter it might be possible to extrapolate the product information to a particular presentation by using other information from the case narrative. When extrapolation of the registered or brand name has taken place, it should be indicated in the case narrative.

When the registered name or brand name (B.2.1) is not known, **the active substance name** should be recorded in the field "Active ingredient(s)" (B.2.2.1) in the section "Active Ingredient(s)" (B.2.2).

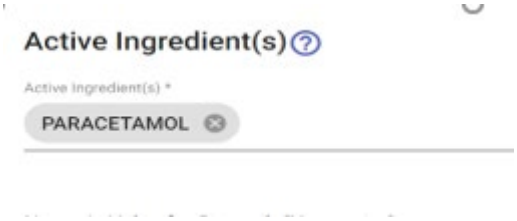
When neither the registered name/brand name or active ingredient is known, despite attempts to collect further information from the primary reporter, the relevant information must only be stated in the narrative. e.g. When the primary reporter has only mentioned a class/form of drug such as "a sedative" or "a local anaesthetic", this information should be stated only in the narrative and NOT in VICH fields. Please note that there must be at least one identifiable medicinal product/active substance in order to achieve a valid suspected adverse event report.

*Example from EVV:*

1.




2.




**IF ONLY THE ACTIVE SUBSTANCE NAME(S) IS/ARE KNOWN, PLEASE RECORD THESE IN THE "ACTIVE INGREDIENT(S) FIELD" AND LEAVE THE "REGISTERED NAME OR BRAND NAME" (B.2.1) FIELD BLANK.**

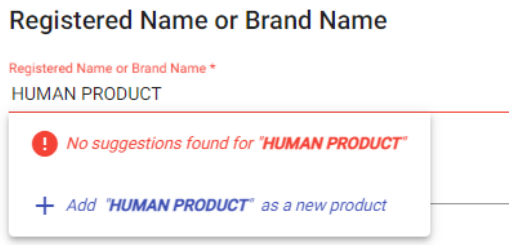
The **Authorisation Number (Registration Identifier)** should always be recorded if known, as in most countries it unequivocally identifies the correct product and presentation.

As the animal(s) might have been treated with more than one medicinal product, the VMP fields under section "VMP(s) Data and Usage" (B.2) are repeatable to allow users to enter data for as many medicinal products as necessary.

The medicinal products used to treat the AE shall not be recorded in the VMP fields. This information shall be recorded in the case narrative. Treatment of AEs can be indicated by VICH Field B.3.7 "Treatment of AE" (yes/no/unknown).

When medicinal products for **human use** are involved, the following information should be recorded in the "Registered name or Brand name" field. When searching, as medicinal products for human use are not included in UPD, the system will display the message below. In this instance, the name of the product can be recorded manually in EVV by clicking on "**Add "Product X" as a new product**". It is recommended to add "(H)" after the "Registered Name or Brand Name" of the product for human use to enable identification and grouping of such products (e.g. Aspirin (H)).

*Example from EVV:*



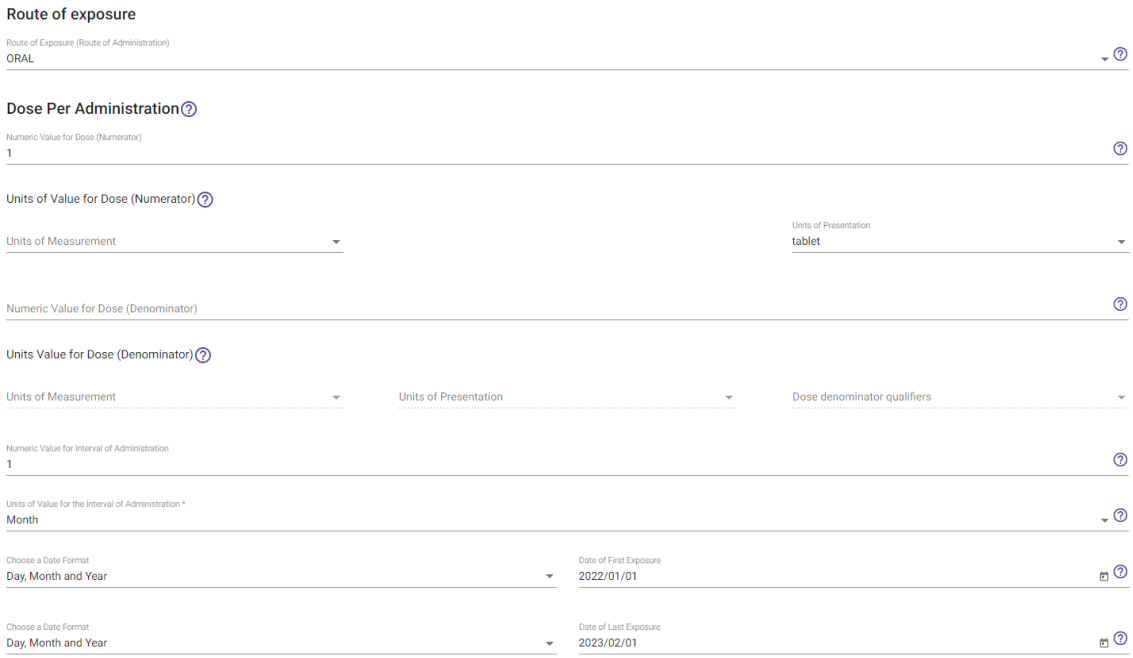

The route of administration (Route of exposure) (B.2.1.7), dose (Dose per administration) and interval of administration treatment should be recorded. These data facilitate the assessment on whether the product was used outside the terms of the marketing authorisation.

If information about Date of first exposure (B.2.1.7.1.3.2) (date of first exposure/treatment) and Date of last exposure (B.2.1.7.1.3.3) (date of last exposure/treatment) is available, it is important to record this information. Please enter the dates as precisely as possible.

The exposure dates and the date of onset of AE (AE start date) (B.3.3) facilitate the calculation of the time to onset of the AE, which is of high importance for the case analysis.

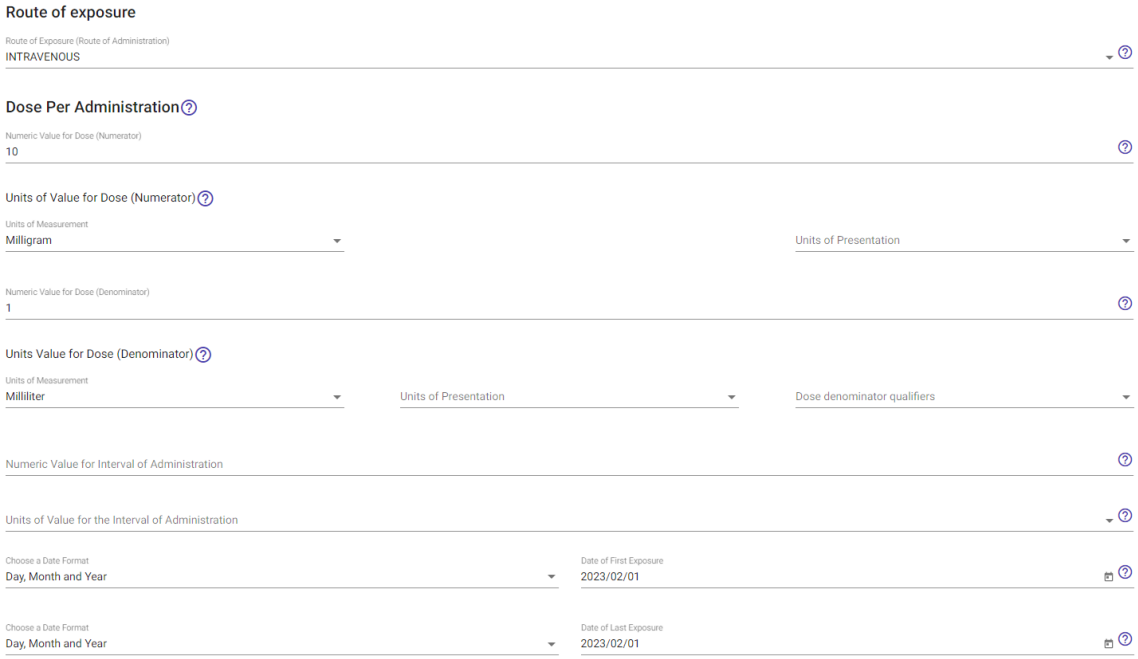
For medicinal products administered at regular intervals (e.g. antiparasitics), the date of first exposure/treatment should be recorded in the 'Date of First Exposure' field (B.2.1.7.1.3.2) and the date of last exposure/treatment should be recorded in the 'Date of Last Exposure' field (B.2.1.7.1.3.3).

*Example with antiparasitics:*




For vaccines, the 'Date of First Exposure' should be the date of the last time the vaccine was administered prior to the date of onset of AE. For example, if the animal experienced an AE after a booster vaccination and the vaccine was administered for the first time one year prior to this, the date of the booster vaccination should be recorded in EVV as the date of the start of exposure/treatment ('Date of First Exposure') and not the date of the initial vaccination and a full explanation should be recorded in the case narrative. The information about any previous exposure to the VMP and any previous AE to VMP should be recorded in the relevant sections (B.3.9 and B.3.10).

*Example with vaccines:*




The field "Length of time Between Exposure to VMP and Onset of AE" (B.3.4) refers to the difference in time between "Date of first exposure" (B.2.1.7.1.3.2) and "onset of AE" in (B.3.3.) (see VICH GL42). The lot number (B.2.3) and the expiration date (B.2.3.1) of the VMP(s) should always be recorded if available.

#### *1.2.2.1. Information that should be recorded in section B.2 VMP(s) Data and Usage*

The information regarding medicinal products or active ingredients to be recorded in B.2.1 Registered Name or Brand Name or B.2.2.1 Active Ingredient, should be based primarily on the information provided by the primary source, i.e. the medicinal products or active ingredients to which the animal, human or environment were exposed prior to the occurrence of the adverse event, and suspected by the primary source to have contributed to the adverse event(s) based on temporal association to the adverse event(s), elimination half-life, the known pharmacodynamic effect or expected duration of effect of medicinal products (e.g. slow-release formulations and long-acting/ depot products). It is recommended in the VGVP module on collection and recording of suspected adverse events for veterinary medicinal products to record in the case narratives which medicinal products/active substances were considered suspected by the primary reporter, when this opinion is available.

Where the notified competent authority or marketing authorisation holder disagrees with the primary source, this should be indicated in the case narrative together with a rationale for recording a medicinal product or active substance in the above-mentioned fields.

It should be noted that all medicinal products or active substances recorded in the relevant VICH-fields, B.2.1 Registered Name or Brand Name or B.2.2.1 Active Ingredient, will be considered for signal detection and analysis in DWH and published, with restrictions, in the public portal of EVV.

#### *1.2.2.2. Information that should only be recorded in the case narrative, section B.3 Adverse Event*

Information on medicinal products or active ingredients mentioned by the primary source and given prior to the adverse event, BUT NOT specifically mentioned or suspected to have contributed to the event by the primary source, is considered important information but should only be captured in the case narrative. As mentioned above, other types of products (e.g. food supplements, biocides) should **only** be recorded in the case narratives.

Where the notified competent authority or marketing authorisation holder disagrees with the primary source, this should be indicated in the case narrative together with a rationale for NOT recording medicinal products or active ingredients in the VICH-fields, B.2.1 Registered Name or Brand Name or B.2.2.1 Active Ingredient.

### 1.2.3. How to record lack of expected efficacy

Lack of expected efficacy (LEE) events, whether or not following use of a VMP in accordance with the terms of the marketing authorisation, should always be reported in the same manner as for other AEs.

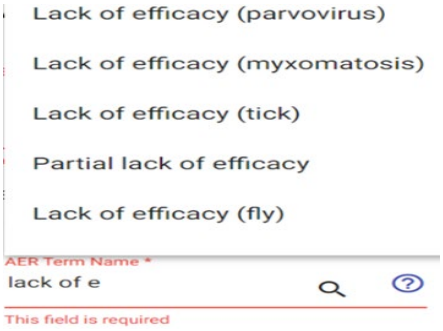
**Recording LEE in EVV:**

All relevant VeDDRA terms should be selected in accordance with the document "Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans".

For AERs with both safety and lack of expected effectiveness elements, the "Type of information in Report" should be recorded as "Both safety and lack of expected effectiveness". The relevant VeDDRA term(s) for the clinical AE sign(s) and the VeDDRA term "Lack of efficacy", SHOULD be selected under "AER Term Name" (see also section 1.1.2).

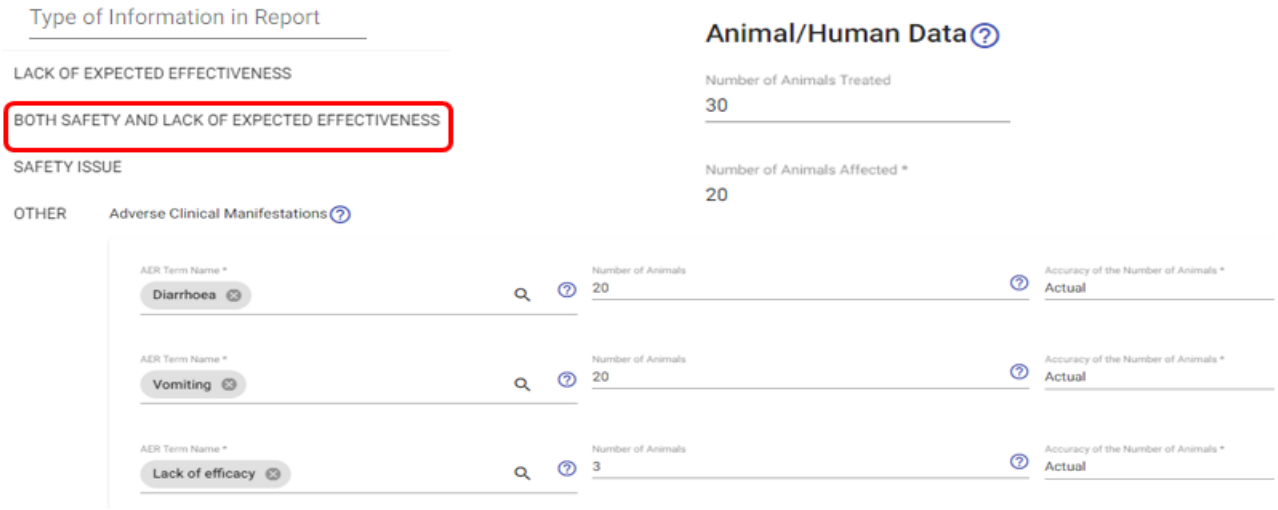
*Type of information in Report:*


*AER Term Name:*



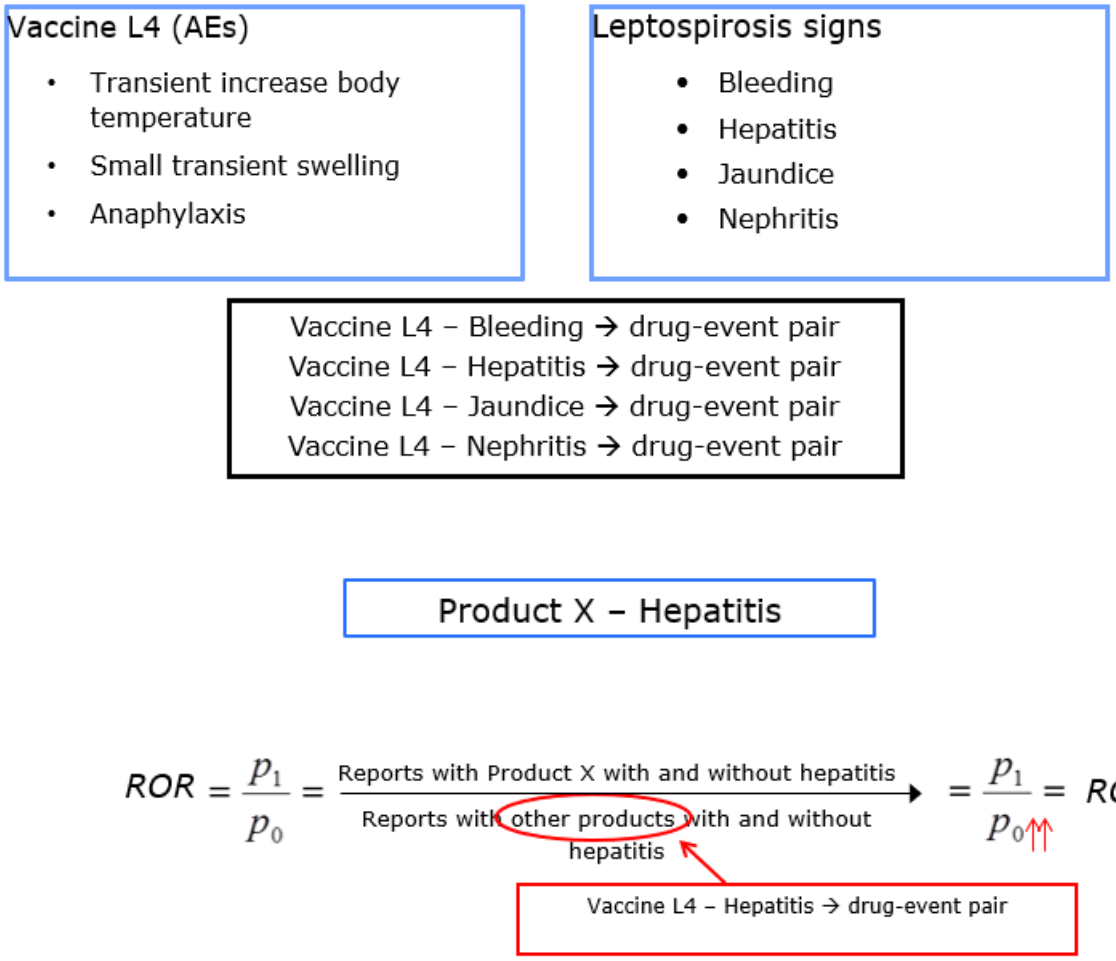

*Example:*

Case narrative: Group of animals, some showing AEs, some LEE: 30 pigs vaccinated with Product X, 20 pigs showed clinical signs (diarrhoea, vomiting) and 3 out of 20 also presented signs of LEE.




For LEE AERs with **no** safety issues, "Lack of expected effectiveness" (LEE) should be selected in the field "Type of information in Report". VeDDRA terms for the disease symptoms **SHOULD NEVER** be coded as AEs (see also section 1.1.2).

**Important note:** Recording signs of the underlying disease or condition as VeDDRA terms may cause these signs to appear as new signals. It may also mask potential signals for other products as shown below:

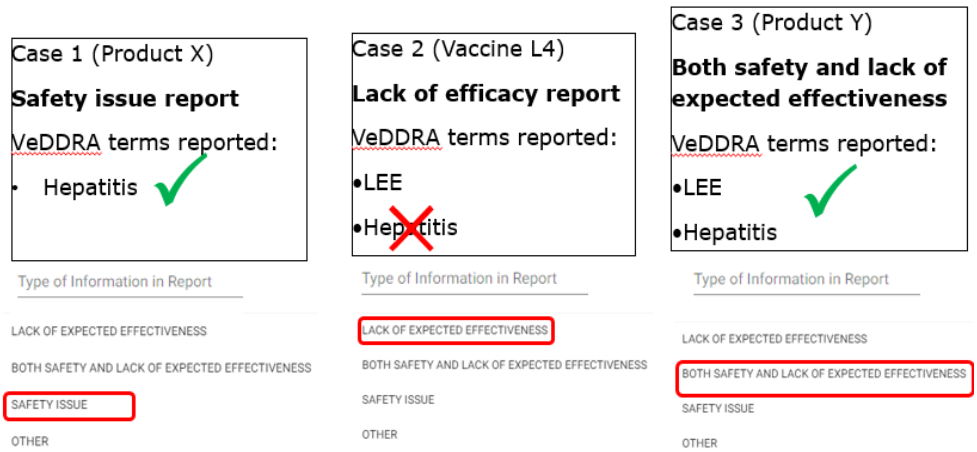



Correct and incorrect coding approach:

Case 1: A VMP (Product X) which is used to treat a disease where the clinical signs do not include hepatitis.

Case 2: A vaccine (Vaccine L4) which is used for Leptospirosis, a disease which causes clinical signs such as hepatitis.

Case 3: A VMP (Product Y) which is used to treat osteoarthritis, a disease where the clinical signs do not include hepatitis. There is lack of efficacy reported, and the animal additionally suffered from hepatitis.



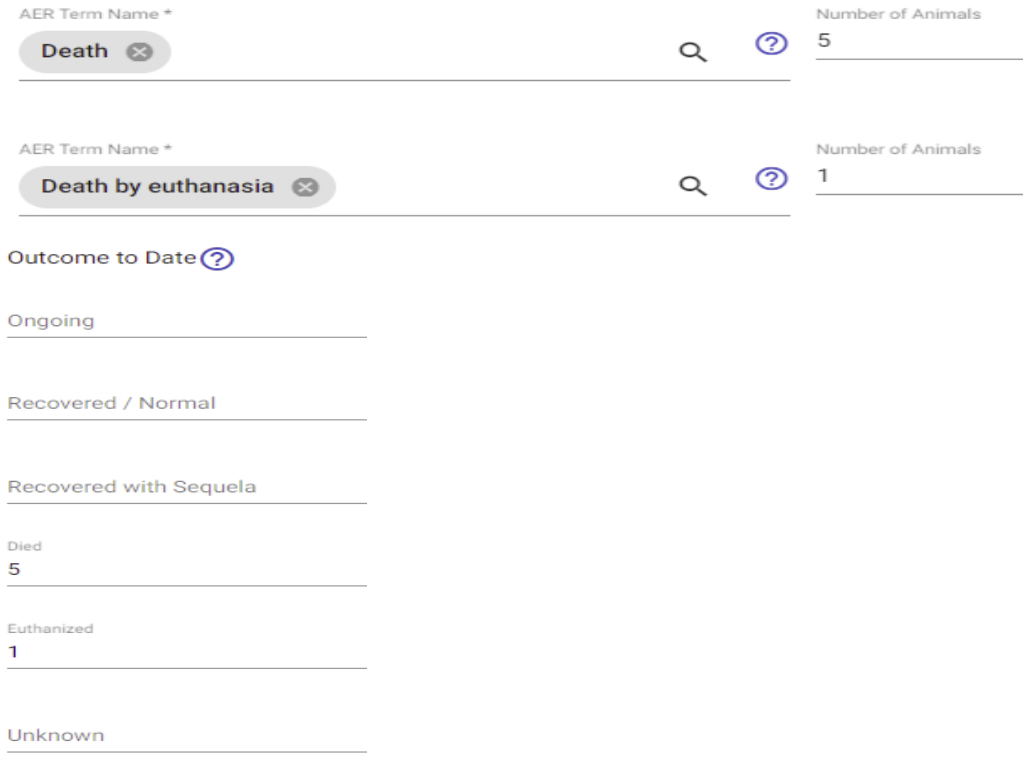
### 1.2.4. How to record death

When recording death in EVV, the AER term(s) should be filled in section "Adverse Clinical Manifestations", using the appropriate VeDDRA low level term(s) (see also the Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans).

The number of animals (actual or estimated) should be recorded against the relevant VeDDRA term(s).

The fields "Died" (B.3.8.4) and/or "Euthanized" (B.3.8.5) in section "Outcome To Date" (B.3.8) should be completed with the relevant numbers.

*Examples:*



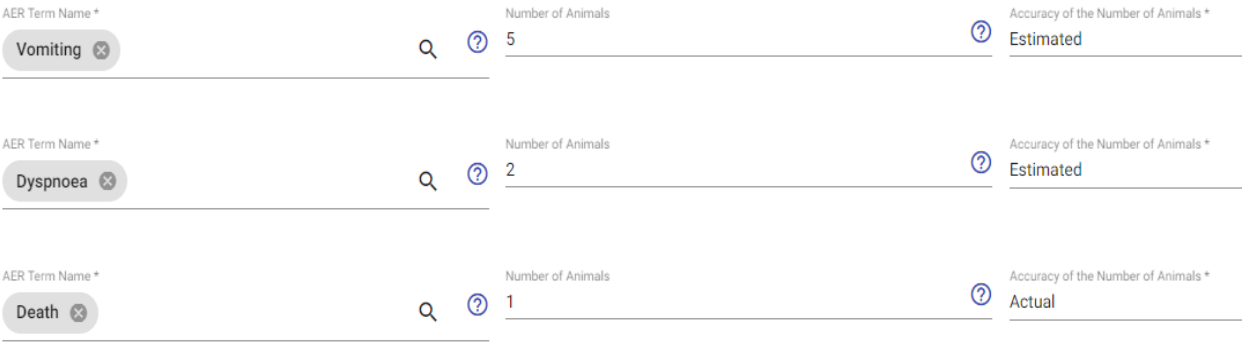

### 1.2.5. How to use VeDDRA terms in AERs

It is strongly recommended that **the latest version** of the document "Combined VeDDRA list of clinical terms for reporting suspected adverse reactions in animals and humans to veterinary medicinal products (europa.eu)" is used, to enable the use of newly introduced VeDDRA terms and optimize coding. It should be noted that the latest version of the Combined VeDDRA list is released on the 1st October of each year.

A complete transcription of the clinical signs mentioned in the case narrative into VeDDRA terms is very important, even if some of the terms that were used in the case narrative are similar, as most of the statistical analysis and signal detection is based on the VeDDRA terms selected. The "AER term name" section (B.3.2) is repeatable, to allow users to enter as many terms as needed. The most specific terms should be selected as appropriate (e.g application site hair loss and not hair loss NOS).

The number of animals affected should be recorded in EVV in the "Number of animals affected" field (B.1.2.) as well as against each VeDDRA term, as clinical signs may differ between animals in the AER.


Note: In case no precise information is available, the number should be recorded as "estimated".




### 1.2.6. When to split AERs

Splitting AERs should be limited as much as possible, and clinical judgement should be applied on a case-by-case basis.

A case concerning multiple animals in the same farm/household that have received different products, with different dates of administration and with different time to onset of AEs **SHOULD** be split and recorded in EVV as separate AERs.

In addition, when an AE occurs after the administration of a treating product (Product 2; administered for treating an adverse event after application of Product 1), then any AE occurring after application of Product 2 **SHOULD** be split and recorded as a separate AER.

Also, a case concerning AEs in different species after simultaneous administration of the same product to animals of the same holding **SHOULD** be split and recorded in EVV as separate AERs.

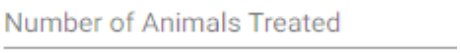
When splitting AERs, it is very important that the AERs should be linked using the appropriate field in the linked report section (B.6). The "AERID" of any other reports which are related to the report can be entered in B.6.1 and the explanation for the linkage should be entered in B.6.1.1 according to what is considered most appropriate for the case. It is also advised that the rationale for splitting is added to the case narratives of the separate AERs.

AERs with the following scenarios **SHOULD NOT** be split:

- Reports with AEs in the same case (i.e. same product(s)) that involve multiple animals,
- Seemingly unconnected AEs in the same animal in the same case (e.g. local skin reaction and blindness),
- Information on VeDDRA terms and outcome information (such as death) related to a single animal should only be included in one AER and never be split.

### 1.2.7. Suspected AEs in offspring exposed through a parent

- The number of animals ***treated*** should ALWAYS be equal to the number of parent animals treated and recorded in the relevant field (B1.1.).




- The number of animals ***affected*** should be recorded in the relevant mandatory field (B.1.2.) as well as against each relevant VeDDRA term.


- The treatment start date should be the date the parent was treated.
- The clinical signs in the case narrative should describe the clinical signs of the offspring as well as of the parent.
- Record the total number of parent and offspring reacting in "number of animals affected"
    - In case of adverse events observed with abortion (Table 1, Case 1), the VeDDRA term "abortion" and its corresponding number should be related to the parent animal(s). The number of aborted animals should only be stated in the case narrative and it should not be counted as number of animals died.
    - In cases of LEE reported for VMPs applied to parent animal(s) and which are indicated to prevent foetal mortality, abortion or transmission of a pathogen to the offspring (Table 1, Case 3), the "lack of efficacy" does not refer to the offspring as the VMP should have been effective in the parent animal(s); abortion, stillbirth or transmission of the pathogen to the offspring should only be considered as indications of insufficient efficacy in the parent animal(s). In this instance, the respective LLT term for lack of efficacy should be chosen where applicable.
    - In case of adverse events observed with stillbirth, the number of stillborn offspring should be recorded against the VeDDRA term "Stillbirth", and these animals should also be counted as number of animals died (Table 1, Case 2).
    - However, when the VMP is indicated to protect the offspring and insufficient efficacy can be assumed in the offspring (Table 1, Case 4), the number of offspring must be entered as affected animals and the number of treated animals still refers to the parent animal(s). This applies for example to vaccines that are administered to the parent in order to protect the offspring by transferring specific antibodies via the colostrum and symptoms of the corresponding disease are observed in the offspring and the suspicion arises that the vaccination has not been sufficiently effective.

| | Case 1 | Case 2 | Case 3 | Case 4 |
|---|---|---|---|---|
| | Adverse event which includes abortion as safety observation | All other adverse events regarding safety observations (i.e. without abortion) | LEE (product expected to be efficient in parent to prevent stillbirth, abortion, transmission of | LEE (product expected to be efficient on offspring – passive immunity) |

| | | | | |
|---|---|---|---|---|
| | | e.g. stillbirth, malformation, etc. | pathogen to the offspring), e.g. PRRS | |
| Number treated | Parents | Parents | Parents | Parents |
| Number affected/died | Parents +/- offspring **Caution: aborted offspring (runts) are not counted as affected and dead animals** | Offspring +/- parents (if also signs in parents) | Parents. Offspring is not counted. | Offspring +/- Parent |
| VeDDRA coding | PT Abortion | Signs on offspring +/- parents | PT Lack of efficacy +/- PT Death (only if related to parent) | PT Lack of efficacy +/- PT Death |

**Table 1:** Possible parent/offspring adverse event scenarios and recording instructions

In the event of, e.g. malformations or congenital disorders in stillborn offspring, the relevant VeDDRA terms (in this example "Malformation NOS" or "Congenital disorders NOS") should also be recorded in the "Animal signs" section and the number of the affected offspring should be recorded if available.

## *1.3. How to avoid creating duplicate reports and how to handle duplicates recorded in EVV*

A review of the existing duplicates in EVV showed that there are two main causes of duplication:

1) Same organisations changing the AERID when sending follow-up reports
2) Same AE involving multiple MAHs or the NCA of the country of occurrence.

The existence of these potential duplicate reports is most likely to be discovered by MAHs or NCA of the country of occurrence when downloading AERs related to their product(s), or when running the signal detection procedure.

To avoid creation of duplicates as mentioned under point 1 above, all organisations should ensure that the AERID is not changed when they record follow-up reports in EVV. *PLEASE NOTE THAT AS AN INTERIM MEASURE FROM 20 JULY 2022 UNTIL FURTHER NOTICE, FOLLOW UP REPORTS SHOULD* ***ONLY*** *BE SENT BY THE INITIAL SENDER ORGANISATION OF THE AER.*

With regards to the second situation, in cases where an animal or a group of animals has been given several veterinary medicinal products concomitantly and the animal(s) experience(s) one or more AEs, a problem might arise where various MAHs and/or NCA of the country of occurrence record information related to the same AE in EVV.

The process for handling of duplicate reports is briefly described in the VGVP module on collection and recording of suspected AEs for VMPs, section 2.11 and in the EU VICH adverse event report implementation guide. A duplicate management tool has been developed in EVV to detect and handle potential duplicate AERs. An algorithm scans the AERs submitted to EVV and ranks them against each other as a pair review in accordance with their similarity, based on predefined parameters and exclusion criteria. These pairs are presented to the data steward via a user interface to allow manual review of the AE pairs, and make a decision on whether they are duplicates or not. If a pair of AERs have been deemed as duplicates, one of the reports is designated as the principal report, and the other is marked as a duplicate. Only the principal report will be subsequently used for analysis in EVV DWH.

EVV users that come across potential duplicate cases when downloading reports or performing signal detection may inform EMA via the EMA Service desk system to enable the data steward to review and link the cases if needed.

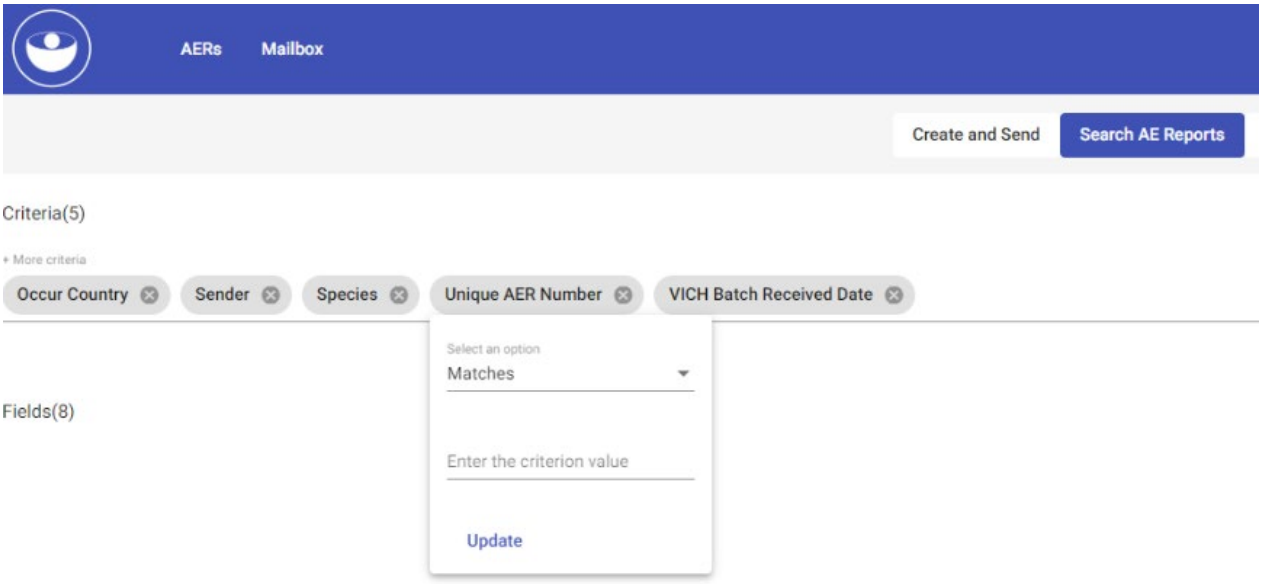
## 1.4. How to nullify an AER recorded erroneously in EVV

In case an AER is recorded erroneously in EVV (e.g. incorrect AERID, or the sender organisation notices that the AER recorded in EVV is not a valid AER, or duplicate AER), the AER can be nullified.

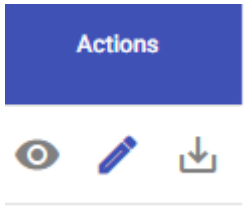
Gateway organisations sending a nullification report should select the entry "NULLIFICATION" in the field "Type of Submission". Once "NULLIFICATION" is selected, the field "Reason for Nullification Report" should be completed with the information on the reason for the nullification (see below).

EVWeb users may retrieve the AER by searching in the "Search AE Reports" section with the use of the quick search functionality (see below).


The AER may also be retrieved by searching in the "Search AE Reports" section by entering the AERID in the criteria section (see below).

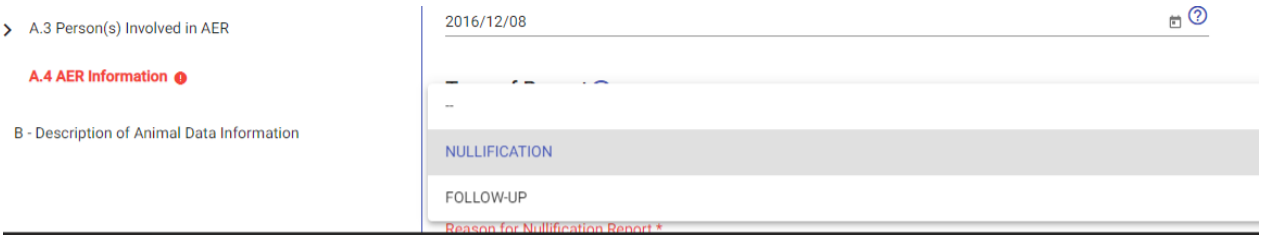



Once the AER is retrieved, the "Follow-up/Nullification" icon should be selected in the "Action" section (see below) in order to transfer the AER to the "Create and Send" section.

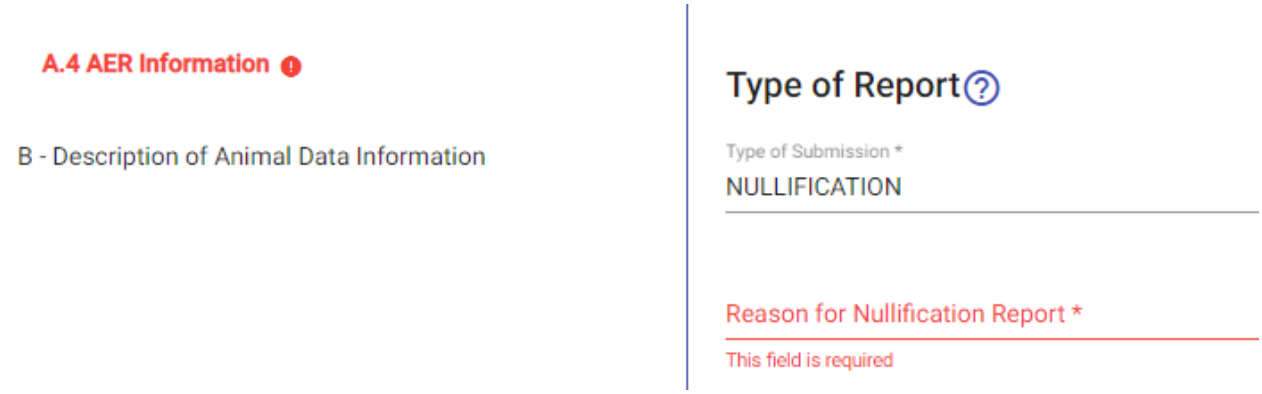



Once the AER is transferred to the "Create and Send" section, "A.4 AER Information" should be clicked and the field "Type of Submission" should be selected in the section "Type of Report" (see below).


The entry "NULLIFICATION" should be selected in the field "Type of Submission" (see below).




Once "NULLIFICATION" is selected, the field "Reason for Nullification Report" should be completed with the information on the reason for the nullification (see below).




The nullification report can now be recorded in EVV.

## *1.5. Recording of follow-up AERs in EVV*

The following business rules apply to the recording of follow-up AERs in EVV (valid from 1st December 2022 until further notice*):

Follow-up AERs can **only** be recorded by the original senders of an initial AER in EVV. Appropriate business rules within EVV have been set up to limit the recording of follow-up AERs. Organisations (NCAs and MAHs) that are not the original sender of an initial AER and consider it necessary to amend an AER, should contact the original sender (MAH or NCA) directly.

All organisations (NCAs and MAHs) remain responsible to ensure a high level of accuracy in their AERs in EVV.

** This limited period is in place to provide the opportunity to re-evaluate business rules and allow for further modification as pharmacovigilance systems adapt.*

Information in data element fields and/or case narratives in AERs from the original sender organisations should **not routinely** be changed, specifically with regards to initial receive date,

product information or information within the case narrative, unless considered significant information that could impact on clinical interpretation and signal management activities in EVV.

When amendments are considered necessary, the overriding principle is that organisations should only record follow-up AERs in EVV if additional **significant new information** has been received for a previously recorded AER as follows:

- **Significant new information** should be recorded in EVV within 30-calendar-days of receipt.
- Any changes should be **clearly** outlined in the case narrative.
- The table below defines significant new information and provides **non-exhaustive** examples.
- **Clinical judgement** should be applied for the identification of significant new information.

However, there may be instances where an AER which has already been recorded in EVV may need to be amended, for example when some elements are incorrect but no significant new information has been received. This may warrant the recording of a follow-up AER in EVV by an NCA or MAH. The same principle would apply where supplemental documents mentioned in the AER, translations or literature articles are requested by an NCA and are subsequently sent as attachment in a follow-up AER. Some of these scenarios are illustrated in the table below.

**IMPORTANT: To avoid the need to record multiple follow-up AERs in EVV, organisations are strongly encouraged to make use of the full 30-calendar day period in order to collect all available information and record in EVV initial AERs with complete and accurate data.**

The following table provides a definition for significant new and non-significant information, as well as a **non-exhaustive** list of examples:

| Type of information | Definition | Examples (not limited to) | Permitted action |
|---|---|---|---|
| Significant new information | New or updated clinical or administrative information on previously recorded AER in EVV that could impact on its clinical interpretation and on signal management activities in EVVET.<br><br>Clinical judgement should be applied for the identification of significant new information. | New reported suspected adverse events i.e. clinical signs, or event of lack of efficacy, residues/withdrawal period issues, environmental issue, transmission of infectious agent. This also could include important VeDDRA terms which have initially been missed.<br><br>New veterinary/human medicinal product(s) or new active substance(s).<br><br>The product name of the veterinary medicinal product has become available (not stated in the initial AER).<br><br>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, have become available. | Follow-up AER recorded in EVV.<br><br>**NB:** Information that has been added should be stated clearly in the case narrative. |

| | | | |
|---|---|---|---|
| | | Change of dates that could facilitate evaluation of the case (e.g. dates of vaccination previously unknown or not according to the case narrative).<br><br>Corrections of typographical errors related to **coded fields**, such as spelling corrections of reported brand names etc.<br><br>Changes in the number of animals treated or affected.<br><br>Insertion or update of lot number.<br><br>Coding of on-/off- label use. | |
| Non-significant information | Changes that do not impact the evaluation or recording of the AER in EVV. | Changes of VeDDRA terms within same PT (unless a clear and significant difference).<br><br>VeDDRA terms that do not change the clinical interpretation of the case. This includes disagreements over VeDDRA coding which should be resolved between parties outside of EVV. Amendment or addition to guidance should be considered in these cases.<br><br>Corrections of typographical errors in the **case narrative** which do not impact on the evaluation of a case.<br><br>Additional information which is set by global requirements from regulatory bodies outside of the EU, such as the addition of "the case is closed" within 3 months of the initial report.<br><br>Addition of contact attempts with the primary source.<br><br>Addition of causality assessment, even if the assessment differs from the assessment provided by the NCA or another MAH.<br><br>Acknowledgement of receipt of an AER within the 30-day obligation. This includes scenarios when MAHs have received duplicates and transmit a Follow-up AER in order to comply with the 30-day obligation. | **NO** follow-up AER recorded in EVV.<br><br>Information should be retained in local databases. This may be verified during inspection<br><br>Information should be conveyed to the relevant NCA/MAH outside of EVV, if considered necessary.<br><br>**For duplicates:** MAHs should record in their own databases the date of identification of the duplicate in EVVET and its worldwide number (this will act as justification for the report not being transmitted to EVVET). |

**Important note related to AERID and submission of follow-up AERs**

The AERID assigned by the original sender of an AER must never be changed when recording a follow-up AER in EVV, regardless of whether the follow-up AER is recorded in EVV by the original sender or by another organisation.

| | |
|---|---|
| **EVWEB users:** | To record a follow-up AER, users should retrieve the relevant AER via the "Search AER" section, click on the "Follow up/Nullification" icon and select the value "FOLLOW UP" on the field "A.4.4.1" "Type of Submission". |
| **Gateway users:** | Organisations should maintain the AERID assigned by the original sender and record the value "FOLLOW UP" on the field "A.4.4.1" "Type of Submission". |

## *1.6. Classification of AERs (see also EU VICH adverse event report implementation guide)*

The versioning of AERs in EVV is also known as "Classification". An AER recorded in EVV for the first time describing a new case (Initial report) is classified as a "Case report". If a follow-up report for the same case is recorded in EVV, the previous version is classified as a "Replaced report", and the follow-up report will receive the status "Case report". When a nullification report is recorded in EVV, the whole case is nullified. With regards to the classification of any previous version(s) of the report, these would become "Replaced reports", and the current version is classified as a "Nullification report".

AERs containing syntactic or semantic errors will be classified as "Error reports".

## *1.7. Reporting adverse event reports (AERs) in EudraVigilance Veterinary (EVV) following the use of immunological veterinary medicinal products (IVMPs) permitted for use within the Union in accordance with Article 110(2) of Regulation (EU) 2019/6*

Article 110(2) of Regulation (EU) 2019/6 allows National Competent Authorities (NCAs) to permit the use of an immunological veterinary medicinal product (IVMP) not authorised within the European Union (EU) in their territory in the event of an outbreak of a listed disease as referred to in Article 5 of Regulation (EU) 2016/429 or an emerging disease.

Since these Article 110(2) IVMPs are not authorised in the EU, they are not included in the Union Product Database (UPD). Nevertheless, the collection of safety information related to these products in a structured and centralised manner is important for the oversight at national level on the use of such unauthorised IVMPs, for the timely and efficient communication between EU Member States on any emerging issue arising from their use and for the future accessibility of AERs reported in relation to Article 110(2) IVMPs, in the context of a possible marketing authorisation application.

**For reporting AEs in relation to Article 110(2) IVMPs it is important that companies responsible for such immunological veterinary medicinal products are following the procedures established by the NCAs which allowed the use of these unauthorised products in their territory in accordance with the provisions of Article 110(2) of Regulation (EU) 2019/6.**

The below guidance is aimed at providing clarity on the data entry requirements and data retrieval for AERs linked to products used under Article 110(2), should companies or NCAs (as applicable, according to national provisions) report them to EVV.

### 1.7.1. Specific data entry requirements for AERs in EVV (via EVWEB or Gateway)

Article 110(2) IVMPs are not authorised within the EU and are therefore not recorded in the Union Product Database (UPD) and therefore not allocated a 'product SN in EVV.

The following naming convention should be followed to optimise data entry and subsequent retrieval:

The name of the IVMP should be entered in the 'registered name or reported brand name' field (VICH field B.2.1) and include the suffix: '(art110.2)'.

**Please note that art110.2 is in lowercase, brackets/parentheses and without spaces. It is important that the 'registered name or reported brand name' is entered consistently i.e. consistent spelling and use of hyphens etc. Any inconsistencies in data entry will impact data quality and thus, affect data retrieval.**

e.g. **Product X (art110.2)**

The name of the company responsible for the Article 110(2) IVMP should be entered in the 'Company or MAH' field (VICH B.2.1.4).

It is critical to include the specified suffix in the name of the unauthorised IVMP in order to avoid the publication on the Adverse Drug Reaction (ADR) website of AE cases submitted prior to the marketing authorisation.

To ensure that such cases reported before the marketing authorisation date are not published on the ADR website, they have to be excluded from the automatic recoding process. This process establishes the link between all reported products in EVV and the corresponding authorised product listed in UPD and subsequently assigns responsibility to the relevant marketing authorisation holder.

A harmonised use of the suffix facilitates targeted searches in EVV and enables easy identification of these products when reported alongside an authorised VMP. This approach allows for manual mapping and recoding against an established placeholder term (e.g. "Unauthorised product"), which will be the entry displayed on the ADR website. This approach enables a transparent view of the products reported in the AER, preventing the identification of the specific product reported prior to its authorisation.

Other information in the AER should be recorded in accordance with VICH standard routines and guidance, including relevant sections of the EVV-BPG.

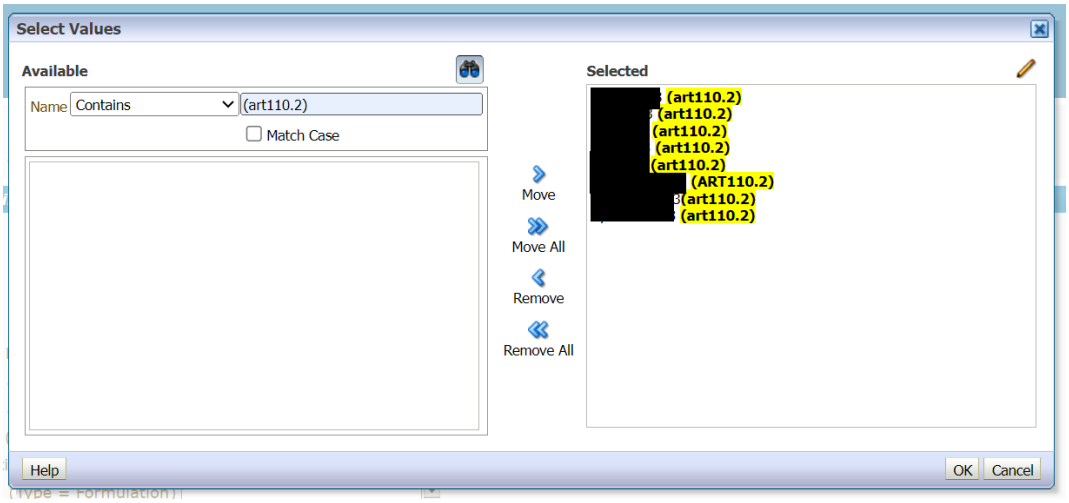
### 1.7.2. AER retrieval and analysis in EVV-DWH

Full case retrieval of AERs for Article 110(2) IVMPs entered using the suffix: '(art110.2)' can only be performed by stakeholders with access level 3. Stakeholders with access level 1 or 2 will not have access to product information (i.e. narrative, name of responsible company, medicinal product code).

It should be noted that the company responsible for the Article 110(2) IVMP will not have level 3 access for their products used under Article 110(2), unless they submit the AER to EVV themselves.

To have full access to the information in the AERs, the company responsible for the Article 110(2) IVMP should contact the NCA permitting its use. As NCAs use different methods to report AERs to EVV (e.g. Gateway user, EVWEB user) the company responsible for the Article 110(2) IVMP and the respective NCA need to agree on an appropriate AER handling and on methods of information exchange between themselves.

AERs can be retrieved from the EVV DWH by searching for 'reported brand name' that contains the suffix: '(art110.2)', see screenshot below.




AERs recorded with the suffix '(art110.2)' will not be combined with any authorised products in EVV and therefore will not be included in statistical calculations (such as ROR) performed in EVV.

Article 110(2) IVMPs which subsequently become authorised within the EU will be included in UPD, according to their authorised VMP name and will be allocated a 'product SN' in EVV.

AERs submitted to EVV prior to granting of the initial marketing authorisation will **not routinely** be recoded to the authorised 'product SN'. However, the recoding to the authorised 'product SN' may be agreed upon on a case-by-case basis.

# 2. Chapter - Practical guidance for VGVP Module: Signal Management

The aim of this chapter is to provide additional practical guidance to all registered user organisations and their individual users to fulfil their signal management obligations in IRIS and EudraVigilance Veterinary Data Warehouse (EVV-DWH). For detailed support related to the use of the business intelligence tool EVVET DWH, the EVVET – Data Warehouse User Manual should be consulted. Brief guidance related to IRIS submissions can be found in IRIS guide for applicants. Please note that some of the guidance below has been previously captured in webinars which can be viewed on the following website: Union Pharmacovigilance Database: webinar on signal detection and analysis.

## *2.1. Pharmacovigilance responsibilities related to Signal management for MAH, NCA and the EMA*

1. The Marketing Authorisation Holder (MAH) is responsible for the pharmacovigilance of their authorised VMPs and shall continuously evaluate the benefit-risk balance and take appropriate measures for their VMPs (Reg (EU) 2019/6 article 77.4). Marketing authorisation holders shall carry out a signal management process for their veterinary medicinal products, if necessary, taking into account sales data and other relevant pharmacovigilance data (Reg (EU) 2019/6 art 81.1). Furthermore, the MAH shall at least once per year, register all results and outcomes of the signal management process, including a conclusion of the benefit-risk balance, in the Union Pharmacovigilance Database (Reg (EU) 2019/6 article 81.2). On the request of a competent authority or the Agency, the marketing authorisation holder shall, within the time limit set in that request,

provide data demonstrating that the benefit-risk balance remains positive. (Reg (EU) 2019/6 Article 58.9).

2. Competent authorities shall lay down the necessary procedures to evaluate the results and outcomes of the signal management process recorded in the pharmacovigilance database in accordance with article 81.2 as well as suspected adverse events reported to them, consider options for risk management and take any appropriate measures referred to in Articles 129, 130 and 134 concerning marketing authorisations. (Reg (EU) 2019/6 79.1)

3. Competent authorities and the Agency may decide to perform a targeted signal management process for a VMP or a group of VMPs (Reg (EU) 2019/6 art 81.3).

Within the European regulatory network, IRIS is the common administrative tool for submission, management and documentation of signals provided by the EMA (IRIS). In IRIS the MAHs register results of the signal management as "signal management submissions" and the outcome of the benefit/risk balance as the "Annual statement". This forms the basis for the evaluation of the competent authorities in accordance with (Reg (EU) 2019/6 article 79.1).

## 2.2. Signal Management using a risk-based approach

In accordance with Commission Implementing Regulation (EU) 2021/1281 (CIR), MAHs shall perform signal management using a risk-based approach and monitor the data with a frequency proportionate to that risk. This should be documented together with other risk management measures in the pharmacovigilance system master file in accordance with Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files (europa.eu). MAHs should always comply with any specific monitoring frequencies which are applied as conditions in the marketing authorisation. However, according to article 19 of Commission Implementing Regulation (EU) 2021/1281, the MAH shall record on an annual basis in the Union Pharmacovigilance Database (UPhV-database), a conclusion of the benefit-risk balance for all VMPs and confirm that the signal management process has been carried out. In practice, this is done by the submission of an annual statement to IRIS by the MAH.

The risk-based approach shall be applied to determine the methodology, extent and frequency of the signal management process and the rationale shall be documented. The risk-based approach shall take into account the following aspects: type of product, length of time on the market and stability of the pharmacovigilance profile (i.e. based on knowledge gained about the safety and efficacy of the product over its full life cycle), identified and potential risks and the need for additional information [CIR (EU) 2021/1281].

Each organisation should determine the appropriate frequency of monitoring the data for each of their veterinary medicinal products they monitor taking into account the above-mentioned aspects. The monitoring frequency (including any changes) and the justification thereof should be documented in accordance with Guideline on veterinary good pharmacovigilance practices (VGVP) Module: Pharmacovigilance systems, their quality management systems and pharmacovigilance system master files (europa.eu)

The appropriate frequency of monitoring may vary with the accumulation of knowledge on the risk profile of a given veterinary medicinal product, taking into account these different aspects further clarified below, including examples of other aspects or characteristics important to consider determining the frequency of monitoring

1. **Type of product.** For certain types of products it is considered necessary to increase the frequency of monitoring because of the nature of the active substance, or any other property inherent to the product or its use, e.g. live vaccines may require more intensive monitoring to control the possible reversion to virulence or recombination with field strains (knowledge in the past), active substances belonging to a new chemical family may require more intensive monitoring at the beginning of their life-cycle because their safety profile is not completely known at that time.
2. **Time on the market (time from authorisation).** Certain active substances have well-established pharmacological and toxicological profiles, while new and innovative active substances have profiles that have only been determined from the limited data obtained from controlled trials during the development of the product. The "time on the market" has often been considered an important criterion to determine whether the use and properties of a VMP is sufficiently known to provide a stable safety profile.
3. **Changes in the number of AERs and/or number of animals reacted received over a given period.** A high number of reported events can be inherent to the type of product (e.g. some NSAIDs), the relative high exposure and use of certain products, or the circumstance in which a product is used e.g. some anaesthetics. An increase in the frequency of AERs and/or number of animals reacted, for an adverse event is considered as relevant new information that may trigger more intensive surveillance monitoring e.g. batch manufacturing problems could lead to a sudden increase of AERs.
4. **Changes in severity of AERs received over a given period.** A change in severity of AERs could be a potential new risk and may warrant a change to the frequency of surveillance monitoring within the signal management process.
5. **New target species / new indication / new route / new formulation or delivery device (also for well-established active substances).** The addition of new target species and clinical circumstances may also affect the risk of a particular product. VMPs with a novel indication/route/formulation/delivery device may require more intensive monitoring. This may also apply to hybrid products which may have different authorisation conditions that may require more intensive monitoring.
6. **Risks to humans.** VMPs classified as potentially addictive to humans and VMPs with particular safety concerns in humans may require more intensive monitoring. AERs related to humans shall always be monitored and may warrant more intensive monitoring
7. **Lack of expected efficacy.** The potential for evolving lack of expected efficacy can be another element that justifies more intensive monitoring. In particular, this aspect has to be considered for antimicrobials, antiparasitics (due to the possible emergence of resistance mechanisms), and immunologicals (coming from authorisation for recent outbreaks).
8. **Information regarding the validity of the withdrawal period.** Findings of non-compliant residues in foodstuffs of animal origin of active substances for which MRLs have been established for substances intended for food producing animals could have a major impact on public health and may therefore require more frequent monitoring.
9. **Potential environmental issues.** These incidences are reported infrequently through pharmacovigilance tools. Hence, few or only one single serious event may trigger more frequent monitoring.
10. **Transmission of infectious agents.** (e.g. MLV or cell-based products or products with problems of contamination in the past)

## 2.3. Data sources for signal management

According to the Guideline on veterinary good pharmacovigilance practices (VGVP) Module: 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 this may include data from outside the EU. Common sources for signal detection may include spontaneous reporting systems, clinical studies and scientific literature. The Union Pharmacovigilance Database, EVV, EudraVigilance veterinary is an important source of information on suspected adverse events and signals with veterinary medicines in the European Union (EU).

Signals may be detected from reports of suspected AEs (case analysis and/or case series), adverse event databases, articles from the scientific literature and/or other documentation provided by MAHs in the context of regulatory procedures (e.g. variations, post-authorisation studies) or their on-going benefit-risk evaluation of VMPs.

Public websites, social networks, media reports or other systems, through which practitioners and animal owners express their experiences with VMPs, may be considered as sources of information. However, the quality of information from these sources may be low, but if the information meets criteria of a valid AER it should be recorded in the Union Pharmacovigilance Database and subject to subsequent signal detection and analysis, where clinical judgement should be used to assess the validity and usefulness of the information. Clinical judgment is an essential component throughout all phases of the signal management process, including the selection of case reports that could supports a potential signal.

The MAHs 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 (in order to calculate the incidence/reporting rate based on animal exposure) (see article 81.1 of Regulation (EU) 2019/6).

Detection of signals is often based on a periodic monitoring of databases of unsolicited and solicited reports of suspected adverse events, e.g. MAH databases, NCA databases and EVV.

Monitoring of databases of suspected adverse events is an established method of signal detection. The monitoring process can be facilitated by statistical summaries of the information received for each "drug-event" combination over defined time periods. This guidance mainly focuses on signals originating from the monitoring of data from adverse event reporting systems, and particularly the EVV.

Regulation (EU) 2019/6 establishes a Union Pharmacovigilance Database for the reporting and recording of suspected adverse events by competent authorities and MAHs and the results and outcomes of the signal management process. To meet these requirements, an upgraded version of the EVV system was launched on 28 January 2022, along with EVV-web, EVV-DWH and then also a new module for Signal submissions in IRIS. In accordance with Article 17(7) of the Commission Implementing Regulation (EU) 2021/1281, the MAH shall conduct at least one signal detection analysis per year for each of their active substances or products in the Union Pharmacovigilance Database. Therefore, this guidance focuses only on the EVV, as a data source within the Union pharmacovigilance database. When statistically analysing the data in EVV-DWH, it is important to consider that the obligation to submit all valid AERs to EVV, only came into effect on 28 January 2022, as mandated by the EU Regulation 2019/6. Prior to this date, only AERs classified as serious were required to be submitted. Nevertheless, data from all relevant sources should be taken into account , and clinical judgement should always be applied when interpretating the information.

## 2.4. Signal detection and evaluation in EudraVigilanceVeterinary DWH

Signal detection should follow a methodology which takes into account the nature of the data and the characteristics (time on the market, target species, exposure) as well as the type of the VMP (e.g. vaccines may for example require specific methodologies).

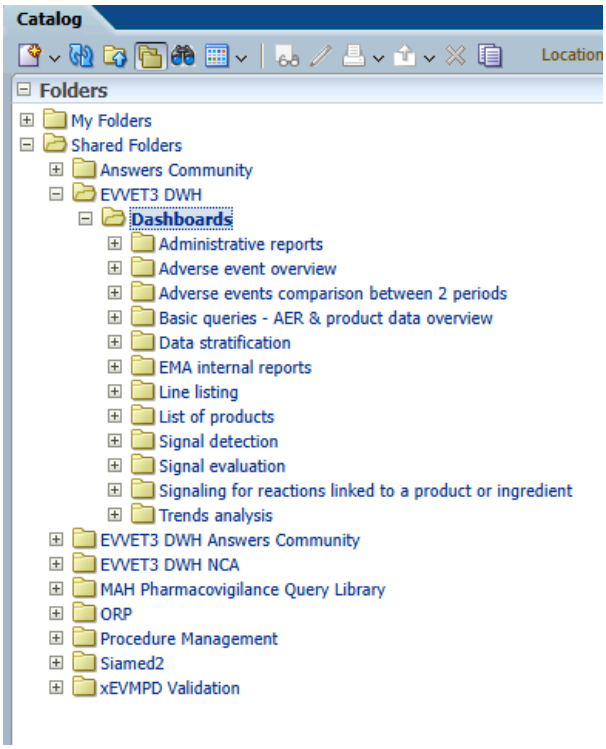
Signal detection is done by performing a combination of statistical analysis and clinical assessment of information coming from AE reports, entered into a database. The signal detection process should be adequately documented by each organisation. Traditional methods of signal detection may be broadly classified into two types: qualitative and quantitative (CIOMs, 2010) Signal detection is depending on the data elements collected and entered into the database. The EVV system uses the VICH standard format for reporting of AEs, where the data elements are harmonised at international level for electronic exchange. However, it should be noted that specifications on how to use a certain field could differ amongst the VICH-regions.

The VGVP for Signal management states that *"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".* Product grouping and 3rd country product names, (including submission of Volume of sales) should be uploaded to the back-end of a separate database, the Union Product Database (UPD). These data are submitted according to the guidance provided in the EU Implementation Guide (IG) on veterinary medicines product data in the Union Product Database - Chapter 7: Submission of other post-authorisation data. These data are not visible to the users of the UPD but are incorporated in EVV-DWH and used in some dashboards as a tool for analysing data by product group.

The EVV-DWH is the module within the Union Pharmacovigilance database that allows stakeholders to detect, analyse and evaluate AE data or subsets of data based on the review of case reports and the application of statistical methods to identify a potential signal related to a VMP(s), class, or group.

According to Article 81(2) of Regulation (EU) 2019/6 and Article 19 of Commission Implementing Regulation (EU) 2021/1281, MAHs are required to record a conclusion on the benefit-risk balance of each of their products in the Union pharmacovigilance database at least annually, thereby confirming that the signal management process has been conducted. This section is supposed to give an example on how this signal management could be conducted. For more detailed instructions on how to use the EVV-DWH and further available queries, please consult the EVVET – Data Warehouse User Manual.

The EVV-DWH offers several dashboards that can be used for signal detection and further analysis, depending on the question raised.



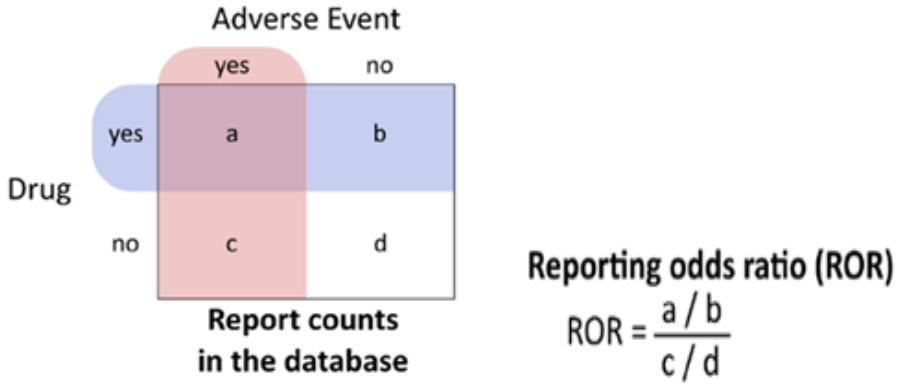

*Screenshot from EVV-DWH highlighting the available dashboards for signal detection.*

### 2.4.1. Signals of Disproportionate Reporting (SDR)

Disproportionality analyses using reports of suspected adverse events are the most used quantitative methods for detecting potential safety signals in pharmacovigilance.

SDR refers to statistical associations between medicinal products and adverse events (drug-event pair). The disproportionality analyses compare the proportion of AERs in those exposed to the drug (proportion "observed") to determine how much it differs from the proportion of the same AERs with the rest of the drugs in the database (proportion "expected").

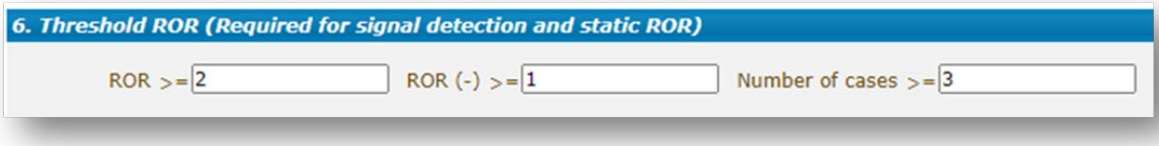
The statistic used to calculate the SDR in EVV-DWH is the Reporting odds Ratio (ROR):




*The definition of Reporting Odds Ratio (ROR) based on the use of the 2 × 2 contingency table.*

The objective of using disproportionality analysis in signal detection is to locate higher than expected frequencies of the "drug-event" pair within the database under the hypothesis that the drug-event combination is reported more frequently for drug X than for other drugs (ROR > 1).

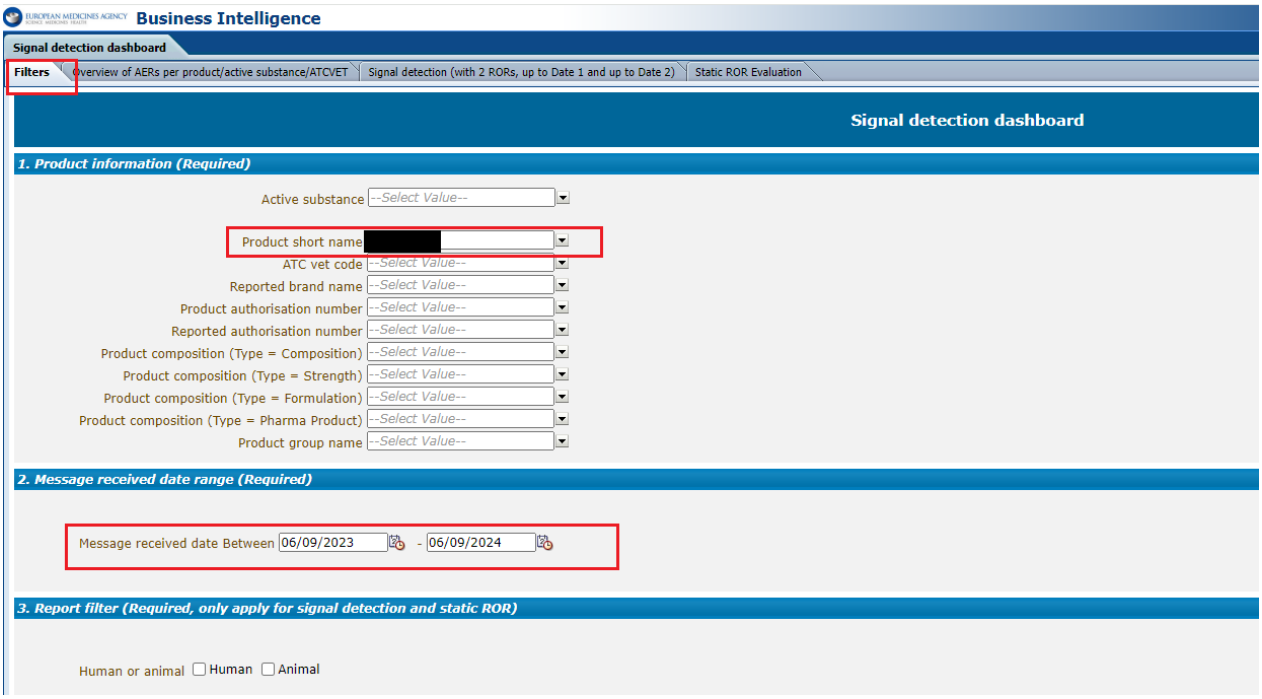
The rules to highlight a SDR in EVV-DWH are the following:



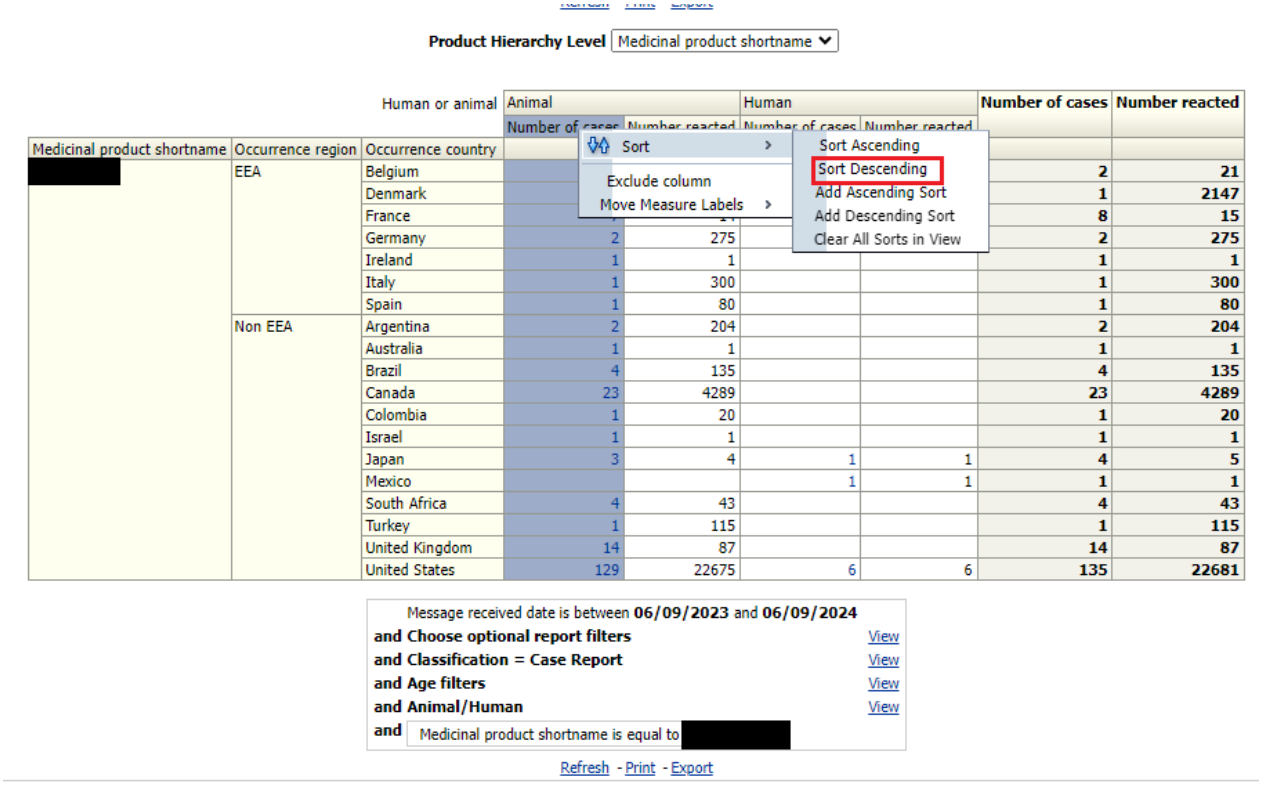

A SDR in EVV-DWH might point towards a possible signal, however it does not imply a causal relationship or establish clinical significance. Thus, it is necessary to take into account that SDRs alone cannot constitute safety signals. SDR is a statistic indicator, and it should be assessed through a case-by-case analysis and contextualised with evidence from other data sources and methods, such as the causality assessment. SDR is a statistical indicator which must be interpreted with caution. While it may suggest a potential association between a veterinary medicinal product and an adverse event, it does not in itself establish causality. Therefore, the SDR should be assessed through a case-by-case analysis, taking into account the clinical content of individual adverse event reports.

In the context of signal detection in veterinary pharmacovigilance, causality assessment refers to the systematic evaluation of the likelihood that a veterinary medicinal product is responsible for an observed suspected adverse event. This process is a critical component to determine whether a reported suspected adverse event is genuinely attributed to a specific drug, rather than being the result of confounding factors or coincidental occurrences. Although the use of the ABON classification system is not currently mandatory within the EVV database for the recording of an individual AER in the database, performing a causality assessment remains essential within the signal management process to ensure that the series of cases considered in the evaluation of a potential signal are sufficiently robust and valid to support the identification and substantiation of a potential safety signal.

The "Signal detection dashboard" of the EVV-DWH is a query that can be used to detect potential signals for a VMP based on SDR. By only entering the product Short Name (SN), active substance or group of products and selecting a time frame, an overview of AEs reported during that time frame in animals and humans can be obtained. Tables can be sorted in descending case number for a better overview.

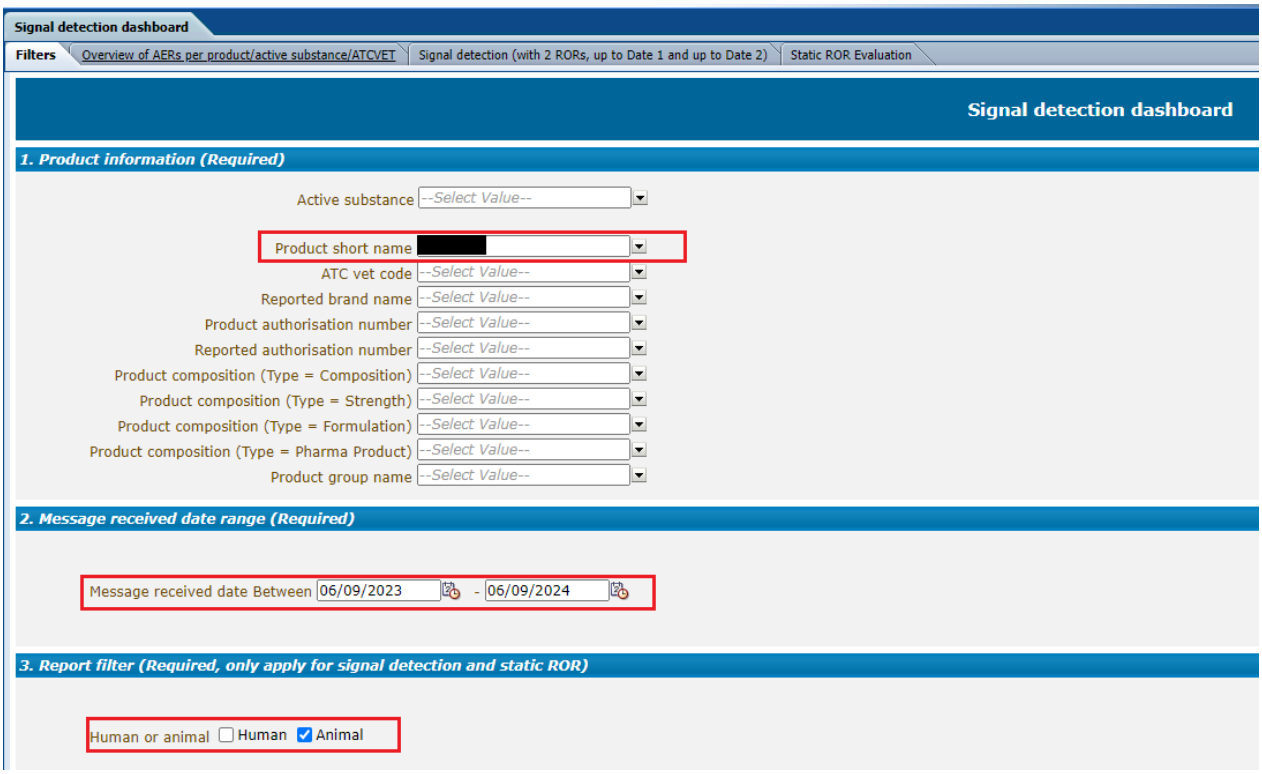



*Screenshot of the Signal detection dashboard in EVV-DWH. The filters tab is highlighted together with the fields for product short name and message received date.*

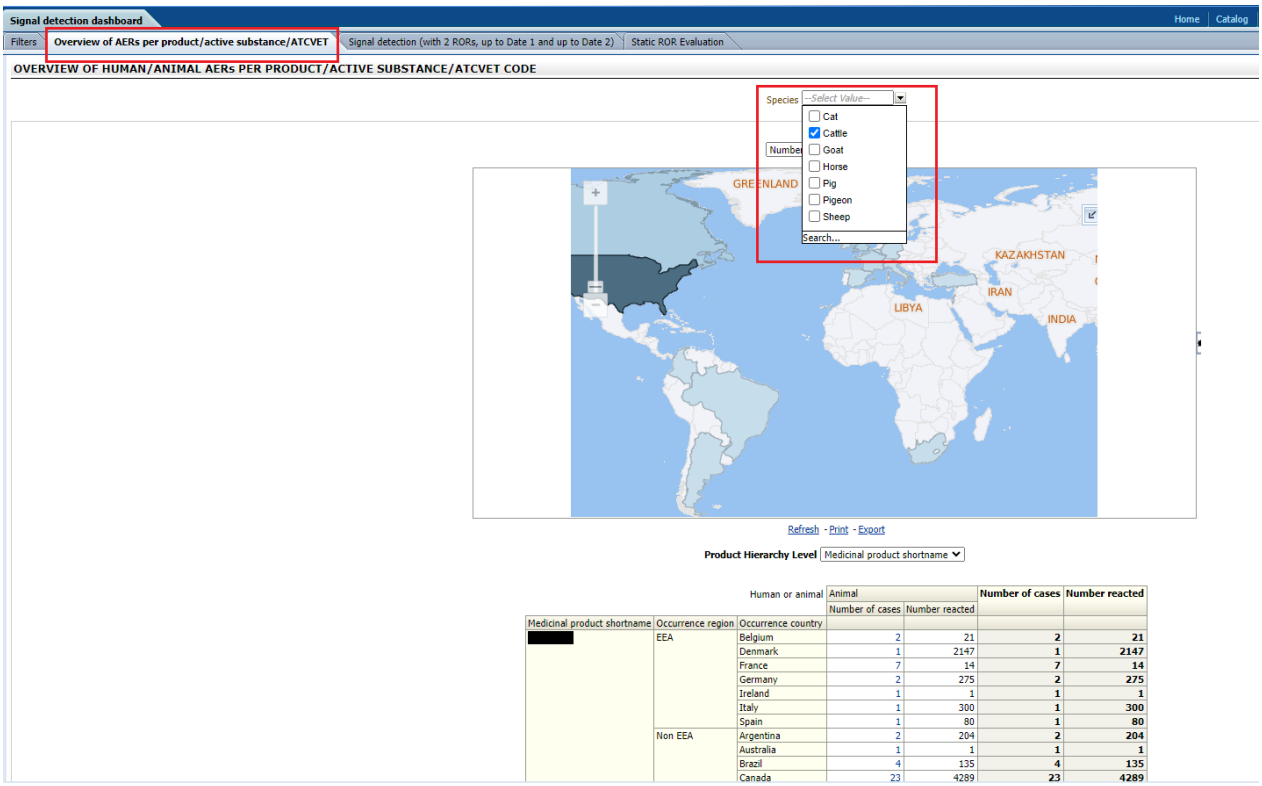



*Screenshot of an output from the Signal detection dashboard in EVV-DWH. The sorting function is highlighted which can be used to facilitate review of an output.*

For Signal detection-query and Static ROR evaluation-query, human, animal or both must be chosen in the report filter. To get an overview of AEs for one VMP, active substance or group of products, it is useful to select "Animal" and thereafter look at the second tab "Overview of human/animal AERs per product/active substance/ATC vet code". In this tab, an overview of AEs that occurred in animals in the respective time period can be obtained. By using the "Species"-filter at the top of the page, different species can be selected, and it is recommended to look at an overview of AEs reported for each species separately. The query also requires to choose to include "All cases" or "New cases" (i.e follow-up reports can be excluded).

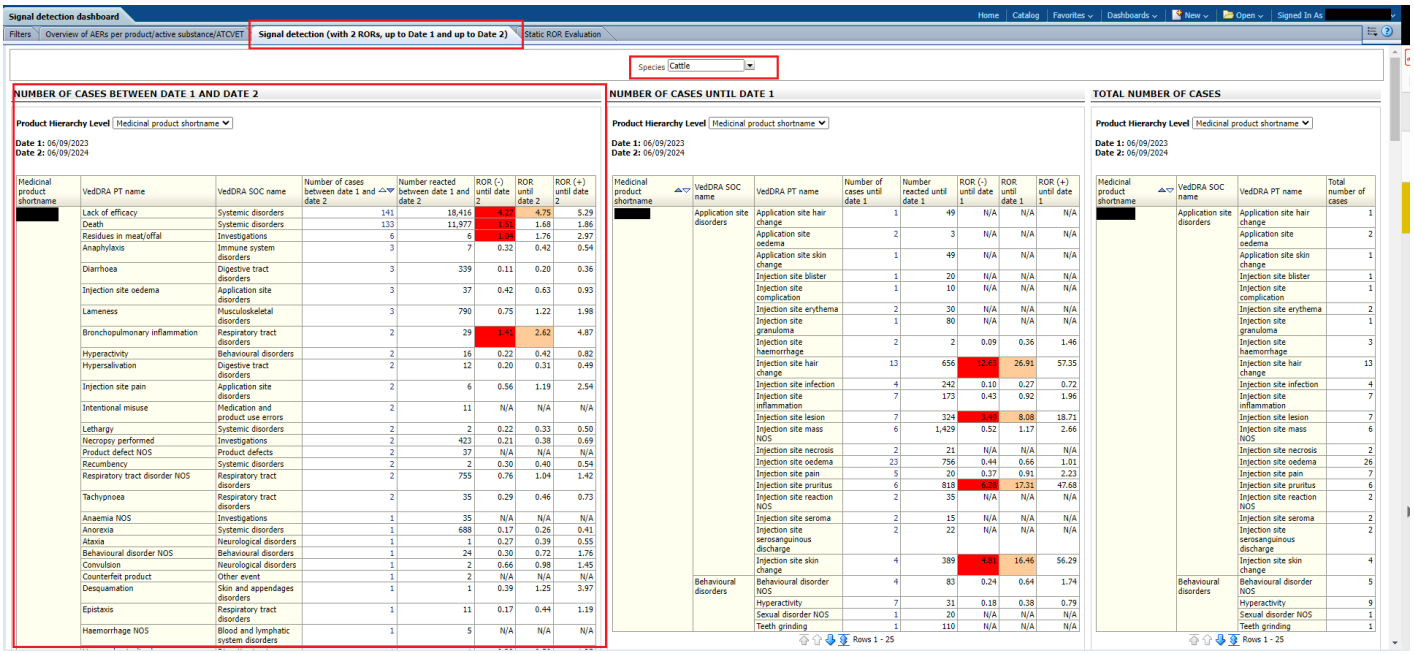



*Screenshot of the Signal detection dashboard in EVV-DWH. The report filter is highlighted for limiting outputs to animal reports together with the fields for product short name and message received date.*




*Screenshot of the Signal detection dashboard in EVV-DWH. The overview of AERs tab is highlighted together with species-filter.*

Depending on the presence/absence/number of reported cases, the third tab (Signal detection with 2 RORs, up to Date 1 and up to Date 2) can be used for a more detailed analysis. As in the overview-tab, a species filter is provided at the top of the page and must be used to look at reported AEs for the individual species affected. A species should always be selected, as potential signals always refer to a certain species. The output is presented in 3 tables, as shown in the screenshot below (table1: Number of AERs between date 1 and date 2, table 2: Number of AERs until date 1, table 3: Total number of AERs)  For table 1, in the left column of this table, the reported VeDDRA preferred terms (VeDDRA PTs) for the selected time period are listed. Nevertheless, it is also important to look at the cases reported before that time period (Table 2, Number of cases until date 1)) and the cumulative number of cases (Table 3: Total number of cases) ). In order to get a better overview of the most frequently reported VeDDRA PTs, the column "VeDDRA SOC name" can be moved to the right and "Number of cases between date 1 and date 2" sorted in descending order. This way, the most frequently reported VeDDRA PTs will appear at the top of the table. The DWH-manual should be consulted for more detailed descriptions.




*Screenshot of an output from the Signal detection dashboard in EVV-DWH. The sort function has been applied to the number of cases column resulting in a descending order of VeDDRA PTs based on the number of cases.*

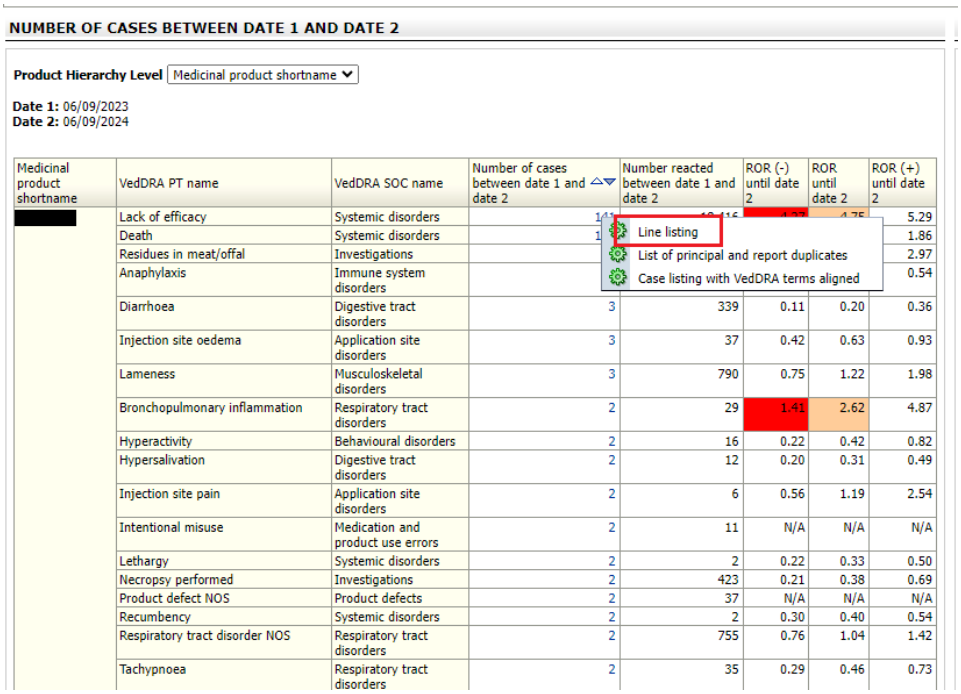
VeDDRA PTs that are potential statistical signals will be highlighted in red, but also VeDDRA PTs that are not statistically signalling can qualify for further investigation, due to the statistical masking effect. Prioritisation of the potential signals allows identifying and focusing on those with a possible significant impact on the benefit-risk balance of the VMP or its active substance or those signals with a high impact on animal or public health or the environment and thus require more urgent attention. As a guide for signal prioritisation, please consult the VGVP-module on Signal Management.

If a VeDDRA PT or group of VeDDRA PTs are qualified for further investigation, it is necessary to have a look at the case narratives to establish the causality in each case ("Line listings" can be obtained by left clicking on the number of reported cases). In addition, all available pharmacological, pre-clinical, clinical, and epidemiological data as well as available literature should be considered in order to assess the potential signal.

In the context of pharmacovigilance, the identification of a potential safety signal requires not only the detection of a statistical or clinical pattern, but also a critical evaluation of the relevance and reliability of the underlying case reports. Causality assessment plays a key role in this process, as it helps determine whether the reported adverse events are plausibly related to the use of the veterinary medicinal product.

While not every individual case must undergo a formal causality classification, especially in large datasets, it is essential to assess whether the available evidence supports a reasonable likelihood of a causal association. This ensures that only clinically meaningful and relevant cases are considered when characterising and validating a signal.

Without causality assessment, there is a risk of overestimating the significance of a signal due to the inclusion of unrelated or poorly documented cases. Therefore, causality assessment—whether qualitative or structured—is a critical step in ensuring the scientific validity and regulatory relevance of any potential safety signal.



**NUMBER OF CASES BETWEEN DATE 1 AND DATE 2**

**Product Hierarchy Level** Medicinal product shortname

**Date 1:** 06/09/2023
**Date 2:** 06/09/2024

| Medicinal product shortname | VedDRA PT name | VedDRA SOC name | Number of cases between date 1 and date 2 | Number reacted between date 1 and date 2 | ROR (-) until date 2 | ROR until date 2 | ROR (+) until date 2 |
|---|---|---|---|---|---|---|---|
| [redacted] | Lack of efficacy | Systemic disorders | 141 | [redacted] | [redacted] | [redacted] | 5.29 |
| | Death | Systemic disorders | 1 | [redacted] | | | 1.86 |
| | Residues in meat/offal | Investigations | | | | | 2.97 |
| | Anaphylaxis | Immune system disorders | | | | | 0.54 |
| | Diarrhoea | Digestive tract disorders | 3 | 339 | 0.11 | 0.20 | 0.36 |
| | Injection site oedema | Application site disorders | 3 | 37 | 0.42 | 0.63 | 0.93 |
| | Lameness | Musculoskeletal disorders | 3 | 790 | 0.75 | 1.22 | 1.98 |
| | Bronchopulmonary inflammation | Respiratory tract disorders | 2 | 29 | 1.41 | 2.62 | 4.87 |
| | Hyperactivity | Behavioural disorders | 2 | 16 | 0.22 | 0.42 | 0.82 |
| | Hypersalivation | Digestive tract disorders | 2 | 12 | 0.20 | 0.31 | 0.49 |
| | Injection site pain | Application site disorders | 2 | 6 | 0.56 | 1.19 | 2.54 |
| | Intentional misuse | Medication and product use errors | 2 | 11 | N/A | N/A | N/A |
| | Lethargy | Systemic disorders | 2 | 2 | 0.22 | 0.33 | 0.50 |
| | Necropsy performed | Investigations | 2 | 423 | 0.21 | 0.38 | 0.69 |
| | Product defect NOS | Product defects | 2 | 37 | N/A | N/A | N/A |
| | Recumbency | Systemic disorders | 2 | 2 | 0.30 | 0.40 | 0.54 |
| | Respiratory tract disorder NOS | Respiratory tract disorders | 2 | 755 | 0.76 | 1.04 | 1.42 |
| | Tachypnoea | Respiratory tract disorders | 2 | 35 | 0.29 | 0.46 | 0.73 |

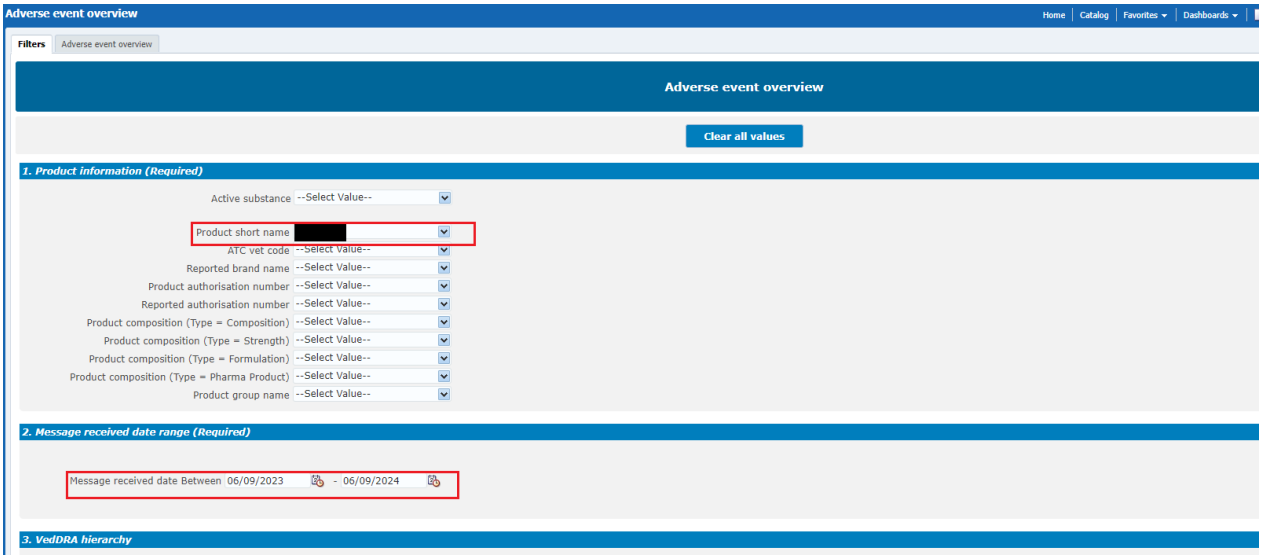


*Screenshot of an output from the Signal detection dashboard in EVV-DWH. The method to retrieve a line listing for a particular VeDDRA PT is highlighted.*

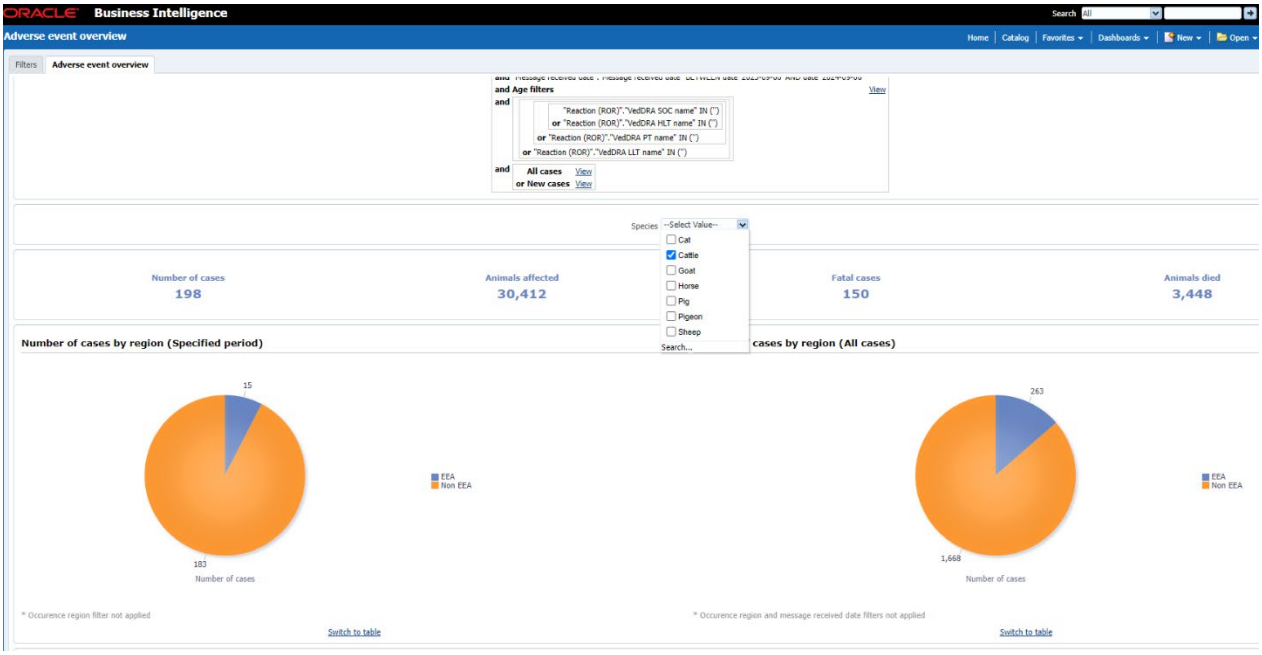
The EVV-DWH offers several other dashboards, besides the "Signal detection dashboard", that can be used for further analysis, depending on the question raised.

Another useful dashboard is the "Adverse event overview" query, which shows the number of cases reported, the number of fatal cases, the number of animals affected and the number of animals that died over the last 10 years, which can be searched by product short name, active substance or group of products. This can also be narrowed down to a specific VeDDRA-term, which can be useful for trend analysis. Moreover, pie charts showing region of occurrence and country for the specified period and all cases can be obtained for the selected VeDDRA term or all reports, if no VeDDRA term is selected.

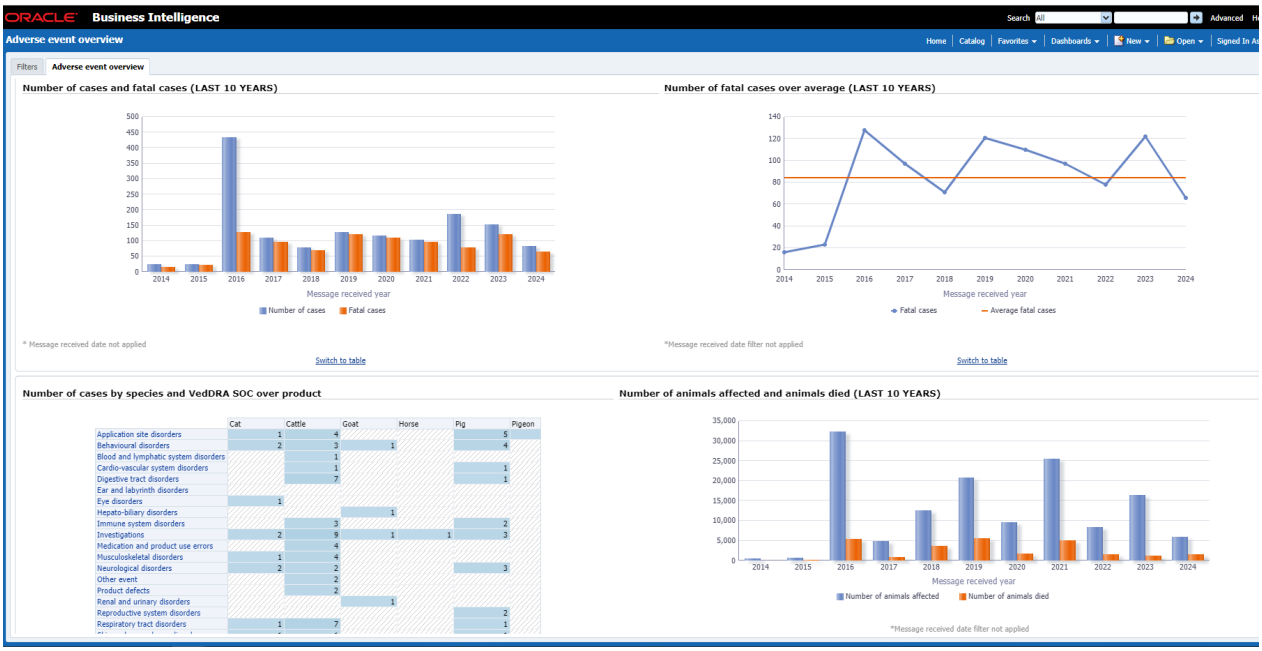
An overview can also be obtained only for a VMP and time period (without specific VeDDRA term selected):




A species can be selected in a drop-down menu at the top of the output page (tab 'Adverse event overview') or alternatively already on the filters tab. By clicking on occurrence-region in the pie charts, this will be further broken down to occurrence country:

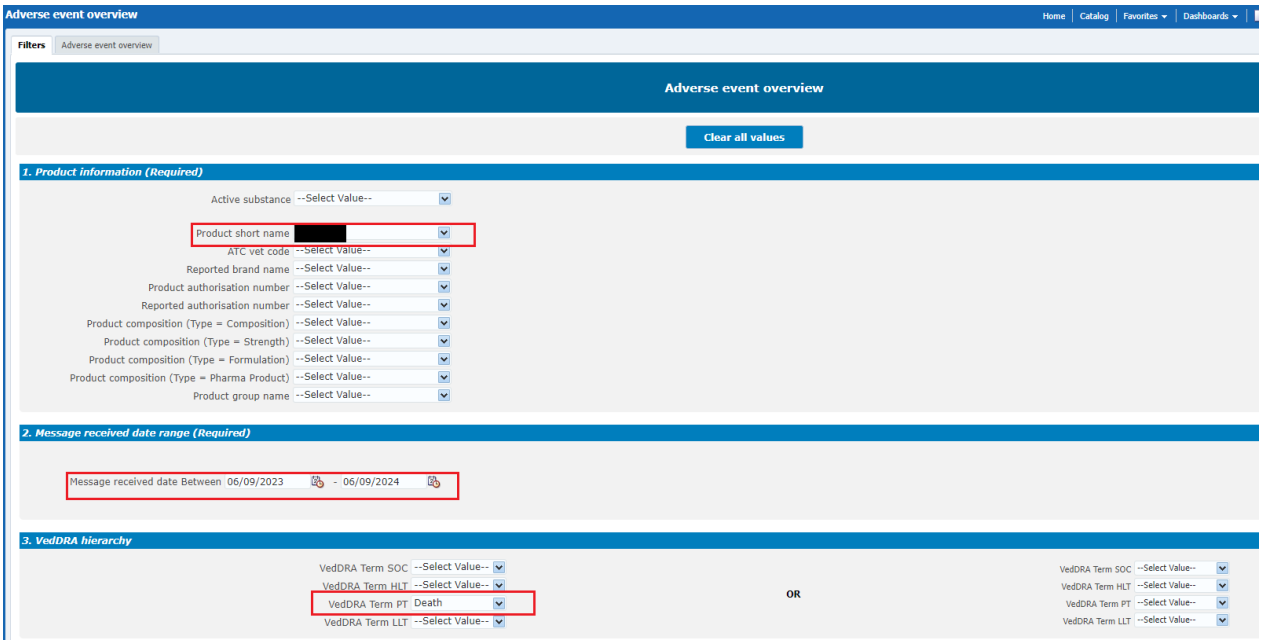


Overview of fatal cases/animals that died over the last 10 years and number of cases reported for the different VeDDRA SOCs sorted by species:




It is possible to get further details of the Overview by clicking of "Switch to table", "See details" or via the links to signal detection reports.

A specific VeDDRA term can also be selected:




Other queries (Dashboard in EVV-DWH) useful for the signal management process are "Data stratification", , "Signal evaluation" and "Trend analysis". A useful overview of the different queries in the EVV-DWH and the kind of information that can be obtained from them is given in section 13: "Dashboard walkthrough" of the EVVET – Data Warehouse User Manual. This section also contains a "standard path" that can be used for a specific product and reaction, highlighting the different queries that can be used to answer specific questions.

## 2.5. Interpretation of statistical results in EudraVigilance Veterinary Data Warehouse (EVV-DWH)

In the EVV-DWH, the data on AERs for VMPs authorised within the EEA are collected and can be analysed in different ways. In addition to a descriptive analysis, the principle statistical analysis in EVV-DWH is to compare the frequency of a specific drug-event pair with the frequency of this specific event associated with other drugs (used as baseline data). This comparison may generate Signals of Disproportionate Reporting (SDR) for drug-event pairs. The interpretation and the applicability of such statistical tools should consider the following:

- Due to the intrinsic limitations of the statistical tool, analyses should only be calculated on an adequately sized dataset. When the dataset is too small, signals may need to be identified based on clinical judgement of cases for a product as statistical approaches may not be sensitive enough.
- A ROR value higher than 1 indicates a higher probability that a specific event occurs in animals treated with the specific product compared to this event occurring following the use of other products. Considering the uncertainty of the ROR values (illustrated by its confidence interval) only ROR values of at least 2 with the lower confidence interval higher than 1 should be considered as having a disproportionate reporting rate. However, events that do not satisfy these criteria for ROR could still be potential signals for other reasons.
- The assessor must take into account the overall breakdown of the data in terms of type of products and type of AEs that are "over-represented", since these make up the denominator value and will influence the ROR significantly and causes a "masking effect". For example,

because the incidence of vomiting in dogs in the database is relatively high due to high reporting and use of non-steroidal anti-inflammatory drugs (NSAIDs) in dogs, the relative occurrence of vomiting for a particular product must reach a similar level to the level seen following NSAID administration before it is detected using ROR.

The use of Reporting Odds Ratio (ROR) as the statistical method for signal detection in EVV-DWH is officially endorsed and operationalized within the EMA's signal detection framework. The application of ROR-based signal detection to the surveillance of VMPs must take into account several particularities linked specifically to veterinary pharmacovigilance, as well as factual elements related to the quality and availability of data:

- The number of individual events may be analysed either by Number of Reports or by Number of Animals. Following implementation of Regulation (EU) 2019/6, it is possible to systematically record the number of animals showing a particular clinical sign, i.e. VeDDRA Low Level Term (LLT) in each individual AE-report submitted to EVV. However, for AE-reports recorded in EVV prior to implementation of the Regulation (EU) 2019/6 on 28 January 2022, it was not possible to consistently indicate the number of animals affected for each VeDDRA term coded in an AE reported , thus this impacts the quality of data available.
- It should be noted that even if data is not submitted to EVV due to previous legislation, such information should still be included in cumulative analyses conducted by the Marketing Authorisation Holder (MAH).
- To cover the period from the last PSUR to the implementation of the Regulation (EU) 2019/6 several MAHs performed a batch submission of former non-serious AERs directly to EVV, which may explain an increase of AERs in 2021/2022 for certain VMPs and adverse events. For the ROR result to be fully relevant, it is essential that the reference population is defined carefully, taking into consideration the specificities of each type of product and event. The EVV-DWHcovers a range of VMPs which are used across different species and populations within species. Also, the reporting patterns vary over time and between geographical regions. Many quantitative signal detection algorithms disregard this diversity which may result in an SDR being masked or in an association being incorrectly flagged as a potential signal. Subgroup analysis could be used to detect a specific AE within a specific subgroup e.g. breed, region or time period. It could be useful to apply data stratification for further analysis. From the Adverse event overview dashboard there is a link to Data stratification report, or the user can access the Data stratification dashboard directly. This is described further in the EVV-DWH manual. Stratification of reports could be useful to adjust the interpretation of the statistical association: for example, to compare whether or not a VMP is significantly more associated with an event than other products of the same class. Animal species is another criterion for data stratification that is essential when dealing with VMPs. Therefore, all the statistical indicators in EVV-DWH are always calculated per species. It may be necessary to select the species in order to retrieve species-specific information.

Signal detection is intrinsically a statistical and observational approach: potential signals emerge from the raw pharmacovigilance data and only allow conclusions to be drawn on the possible statistical association between the use of a VMP and the occurrence of a given event or type of event. This type of alert must not be seen as a "turnkey" solution, as a statistically significant drug/event association may in fact not be clinically significant or may be due to the underlying illness or other biases. Therefore, further steps of signal validation and analysis will be essential as prerequisites to any decision making. Analysis based on ROR calculations can result in both false positive (inherent to this type of mathematical calculation) and false negative outcomes (for example due to the pre-set

thresholds (n>3) where for example some drug-events will not potentially signal based on ROR but is considered a potential signal anyway).

## *2.6. Special considerations during the signal management process*

### *Prioritisation/Validation/Assessment/Confirmation/Recommendation for action*

Throughout the signal management process, it is important to keep in mind the specificities of the use of VMPs in veterinary practice, among which (but not limited to) are the following:

- a single AE-report in animals may involve several animals treated and/or affected. In some cases, a whole group or herd may be affected by herd treatment. Therefore, a "case report" does not necessarily refer to a single affected animal. Data can therefore be analysed by grouping the events of all animals involved in the same AE-report or by taking into account each animal showing a particular clinical sign. For VMPs used to treat large herds, those AE-reports should be considered to be analysed on an individual basis taking into account the number of animals reacting.
- special attention should be paid to AERs referring to some special situations within veterinary pharmacovigilance subject to reporting in the same way e.g. investigations of the validity of the designated withdrawal period, environmental issues;
- specific queries in the EVV-DWH may be used to allow stratification to compare signals calculated with or without certain VMPs or group of VMPs;
- signal prioritisation should be performed throughout the whole signal management process, and criteria for prioritisation of signals is described in section 2.3 of the VGVP for Signal Management.analysis may be confounded by ongoing disease in individuals i.e. it may be considered that an AE might be regarded as a clinical sign of the disease that the product has been administered for and not as an AE caused by the product itself. However, it is important to consider that when the AE is typical for the indication, it may also denote aggravation of the disease and clinical judgment should be used;
- time to onset of the AE, mode of action of the active substance and/or pharmacokinetics of the VMP should also be taken into consideration when analysing and assessing potential signals;
- death is an outcome and signals involving death should be investigated and linked with the potential cause/causes of death (e.g. death due to anaphylaxis, renal insufficiency, gastrointestinal perforation, etc.);
- statistical masking should be considered i.e. a lack of an increased ROR does not mean that a causal association between the VMP and the AE does not exist. It could be the result of a masking effect due to another VMP having a very high number of AE-reports for the particular VeDDRA term, see also section 1.2. Clinical judgement should therefore be used.

## 2.7. Validated signals to be recorded in IRIS

All validated signals should be assessed and submitted to IRIS (by the MAH) with the appropriate outcome (i.e. signal to be refuted, for close monitoring or further regulatory actions needed) .

Validated signals submitted in IRIS should be accompanied with a full assessment report involving a cumulative review of relevant AE reports, not just those cases reported in the period selected but also all available cases since the marketing authorisation date, and to consider any additional evidence considered relevant for this signal. MAHs should use the Veterinary Signal Assessment Report to provide their assessment of all validated signals detected from the EVV or from any other sources, including the MAH's own database.

Non-validated signals should not be submitted to IRIS. The outcome (including analyses, decisions, and rationale for not validating the signal) for non-validated signals should be documented, recorded and stored locally at the MAH site, and kept ready for inspections, according to their quality management system requirements (as described in their PSMF).

Signal validation involves evaluation of the data supporting the detected signal in order to verify that the available documentation contains sufficient evidence demonstrating the existence of a new potential causal association, or a new aspect of a known association, and therefore justifies further evaluation of the signal.

When validating signals, not all VeDDRA PTs highlighted in red, i.e. ROR(-) >1 and ROR > 2 (red and orange), in the EVV-DWH should be considered as validated signals immediately. First, as explained in the VGVP Module Signal Management, to validate a signal, the adverse events should, as minimum, not be already adequately addressed in the current product information, the signal should not be based on duplicate reports, and there should be a temporal association between product administration and the reported events.

Thus, the information to be reviewed in the validation phase of a signal should include all of the following:

- The true number of adverse events reported (i.e. exclusion of duplicate and invalid cases, and cases for which when reading the case narratives, it becomes clear that the event is not related to the VMP in question but can instead be linked to a concomitantly administered drug or the onset of the adverse event was before administration of the VMP in question);
- The animal's demographics (e.g. species, age and sex);
- The suspected medicinal product/active substance (e.g. dose administered/potential off-label use);
- The adverse event (e.g. signs and/or symptoms included in PI or not);
- The temporal association (e.g. event occurred after exposure, but within known pharmacodynamic period of the drug) and
- Cases which are unlikely to have a causal association with the product based on for example clinical outcome in relation to VMP continuation or discontinuation; presence of alternative causes for the adverse event; reporter's and/or MAH/NCA evaluation of causality or plausibility of a biological and pharmacological relationship which allows for such cases to be excluded during signal validation.
- There is no requirement for causality assessment on individual AERs in order to be able to record/submit the case in EVV. However, it is of importance in supporting safety signals, where the focus in on causality rather than plausibility for several key reasons:

- causality assessment aims to determine whether a specific drug caused or contributed to an adverse event.
- regulatory decisions (e.g., label changes, warnings, or drug withdrawals) require evidence of a causal relationship, not just that the event is plausible.
- plausibility refers to whether something is possible or believable based on current knowledge. While an event might be biologically or pharmacologically plausible, that doesn't mean the drug actually caused it. Plausibility is often subjective and insufficient for regulatory or clinical decision-making.
- causality Supports Signal Validation. In pharmacovigilance, a safety signal is a hypothesis of a potential risk. To move from a validated signal to a validated risk, we need causality assessment—a structured evaluation of the likelihood that the drug is responsible

If the signal is found to be based on validated information, and there are still enough reports or suspicions to warrant further investigation, the signal should be considered validated, and further assessment can commence. The result of this further assessment should be recorded in IRIS, with a conclusion to either refute the signal, closely monitor the signal, or a proposal for regulatory action (e.g. update of the product information).

Signals requiring further regulatory actions should be submitted in IRIS using the Veterinary Signal Assessment Report template (signal assessment report template). For signals with the outcome 'Amendment of the PI' a VRA.G.I.19 should be submitted, in parallel

## *2.8. Screening procedure during validation of signals*

In order to facilitate the understanding of the identification of validated signals which require recording in IRIS, the following step-by-step approach has been elaborated. These steps can be applied to identify signals for validation following the signal detection activities using the pre-defined queries in EVV-DWH .

1. Identify drug-event pairs that might need urgent attention. e.g. high numbers of animal deaths, MI VeDDRA terms, or human reports.
2. Identify VeDDRA terms that are adequately addressed in the product information. These AEs would in principle be considered non-validated signals, unless the cases provide evidence suggesting a new aspect of the known risk, e.g. higher frequency, longer duration, more severe outcome, etc.
3. For generic products, if the VeDDRA term(s) is adequately reflected in the PI for the reference product, it should be considered a harmonisation issue and be handled by appropriate variation procedure. Harmonisation issues should can still be considered as validated signals and should then be submitted to IRIS with the proposed outcome.
4. Identify signals already recorded in IRIS i.e. refuted and for close monitoring. Close monitoring signals should be updated, see section 2.4. In case of previously refuted signals, consider whether the new information obtained in the meantime could potentially change the outcome.
5. Identify which VeDDRA terms should be investigated. It is important to consider the relative frequency, nature and severity of VeDDRA terms. The initial focus should be on drug event pairs that fulfil at least one of the following criteria:
    a. ROR(-) >1 (red) and ROR >2 (red and orange) in EVV DWH

b. MI VeDDRA terms with >3 new reports

c. Non-MI VeDDRA terms with many cases and/or large numbers of reacting animals (higher than usually seen for the respective VMP).

For certain products, the number of potential signals identified using the above criteria might be high, thus in these cases it is recommended to prioritise further, see section 2.3 of VGVP Module: Signal Management. A risk-based approach can be used to prioritise which signals deserve more attention and are to be validated first, considering any of the following criteria:

- The adverse event(s) is/are considered serious e.g. there are fatal cases reported, it involves MI VeDDRA term(s), it can potentially affect the benefit-risk balance of the product, or it is clinically relevant (see below communication to animal owners or veterinary/healthcare professionals).
- There should be evidence showing a potential causal association, e.g. there are a high number of cases or animals affected, or there is an unexpected or sudden increase in the number of cases or animals affected; there is literature evidence, biological and pharmacokinetic plausibility, short time to onset, or cases with positive dechallenge or rechallenge. Consider also patterns of AERs (e.g. similar time to onset, similar clinical signs reported, similar subgroup of patients affected, use of products etc).
- The communication of this/these event(s) in the PI would be relevant to an animal owner or veterinary/healthcare professional with regards to risk management; e.g. it would change the decision of the veterinarian whether to prescribe the product, it would give information on what to do in case of occurrence of the event, it would avoid further (diagnostic) interventions in the treated animal, or it might be important information to the client when discussing treatment options.

## *2.9. Annual Statement and Veterinary Signal Management submissions in IRIS*

In accordance with Art 81 of Regulation 2019/6, MAHs are required to record at least annually all results and outcomes of the signal management process, including a conclusion on the benefit-risk balance. For these purposes Annual Statements (AS) and Veterinary Signal Management (VSM) submissions were created.

The Annual Statement is the confirmation that the MAH has performed the signal management process for their VMP(s) and that the benefit-risk-balance remains positive. Any signals which were identified, validated and assessed by the MAH are to be submitted as a Veterinary Signal Management submission, using the respective templates (signal assessment report template).

Annual statements and veterinary signal management submissions should be recorded in IRIS in accordance with the IRIS guide for applicants. To facilitate annual submission of the AS, a list of recommended due dates has been created and published on the EMA website: Due dates submissions annual statements. For VMPs where no signals were detected and validated between due dates, the submission of the AS in IRIS is considered sufficient. The AS should be submitted at the latest, on the recommended due dates. According to the VGVP for Signal management, 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 IRIS by the annual due date, at the latest. No signals should be submitted within the annual statements. In situations where the MAH has knowledge of additional information as defined in section 3.4 of the VGVP Module Signal Management, this information can be submitted with the AS.

It is acceptable to submit multiple clinically relevant VeDDRA PTs in one VSM Application form and signal assessment report only if they are related to the same signal submitted. e.g. cardiac signs such as arrhythmia, bradycardia & heart block could be grouped, analysed and submitted together, see also section 2.3. In any other case (i.e. when the different VeDDRA PTs are not related), the MAHs should submit each VeDDRA PT as a separate signal submission in IRIS.

## 2.10. VMP groupings and annual statements in IRIS

To limit administrative burden, it is permitted to group the same or similar products from the same MAH and submit a grouped annual statement. However, it is not permitted to group products that are not the same or similar e.g. pharmaceutical and immunologicals. Note that different immunologicals should not be considered same/similar and should therefore not be grouped. The definition of same/similar products to be used for grouping of products is outlined in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) Guideline 24.

No further information should be provided with annual statements i.e. no documents should be uploaded as these will not be reviewed. Any relevant documents should be submitted with signal submissions only.

## 2.11. Grouping of VeDDRA PTs in VSM submissions in IRIS

As stated in section 2.3, it is permitted to group relevant/related VeDDRA PTs in the same VSM submission in IRIS. It is important to even take into account related VeDDRA PTs during the analysis of potential new signals; e.g. VeDDRA PTs "Blindness" and "Impaired vision" may be analysed collectively in order to provide all relevant information for assessment. In some situations, it may be relevant to choose a higher VeDDRA term, e.g. HLT.

Another common example is the assessment and analysis of anaphylaxis in target species. It should be considered to group relevant VeDDRA PTs concerning the common clinical signs of the target species as stated in section 3 of Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans (europa.eu). Analysis and assessment of anaphylaxis should not be solely limited to the VeDDRA PT "Anaphylaxis" due to possible differences in coding practices between organisations. This principle can also be applied to analysis and assessment of hypersensitivity reactions.

In some situations, it is important to consider both VeDDRA terms related to the clinical signs or disease and the diagnostic investigations undertaken. The relevant VeDDRA terms should be grouped during analysis and assessment. Subsequently, grouping of relevant VeDDRA terms can be considered when generating a VSM submission in IRIS.

## 2.12. Signal assessment and outcomes in IRIS

In order to facilitate the assessment of the validated signals, the standardised Signal Assessment Report Template (current version in the EMA website - link) should be completed with the relevant information, as applicable. The use of the EMA's Signal Assessment Report Template is necessary to ensure standardisation, regulatory compliance and high-quality evaluations of safety signals. It promotes consistency, improves communication, and supports effective pharmacovigilance decision-making

Veterinary signal management (VSM) submissions should be recorded in IRIS in accordance with the IRIS guide for applicants. The Signal Assessment Report Template should be included with the

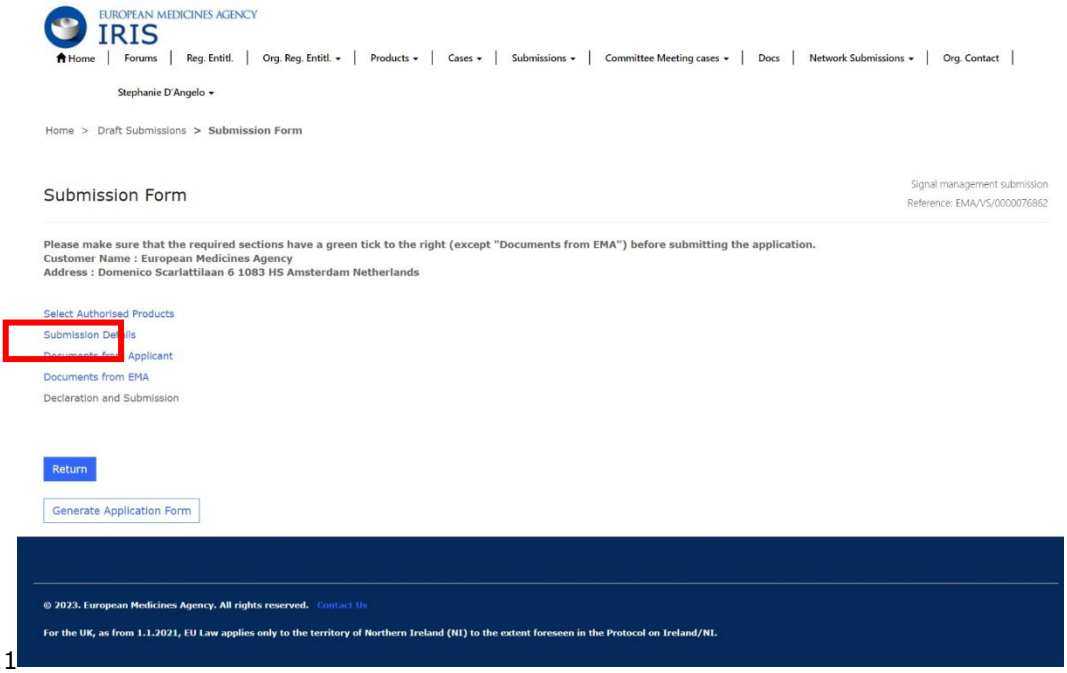
Application Form – Signal management submission, for all validated signals, including those proposed to be refuted, those proposed for close monitoring and those for which regulatory action and/or risk minimisation measures are proposed (e.g. PI update, PASS, educational material, etc.)

The VGVP states that a signal submitted to IRIS could be 'closed' without the need for any additional regulatory actions (i.e. routine pharmacovigilance activities will continue to be performed). However, such functionality is not currently available in IRIS.

## *2.13. Providing Updates on signal submissions in IRIS*

As stated in VGVP Module: Signal Management, for signals that are considered under close monitoring and which were already submitted more than six months prior to the due date, a completely new signal submission should be submitted in IRIS with the focus on the review of any new evidence available since the last signal submission. An updated conclusion and proposal for action should be provided which should take into account the previous cases and evidence reviewed. Note that it is not possible to update or amend previous signal submissions. Any changes or additions can only be recorded in IRIS through a completely new signal submission.

It is important that this new signal submission is linked to the previous signal submission(s) in order to identify the new submission as an update to the previous one. Signal submissions can be linked to previously submitted signals using the "Link Previous Submission" function in IRIS, see screenshots below. This function is found under "Submission Details".

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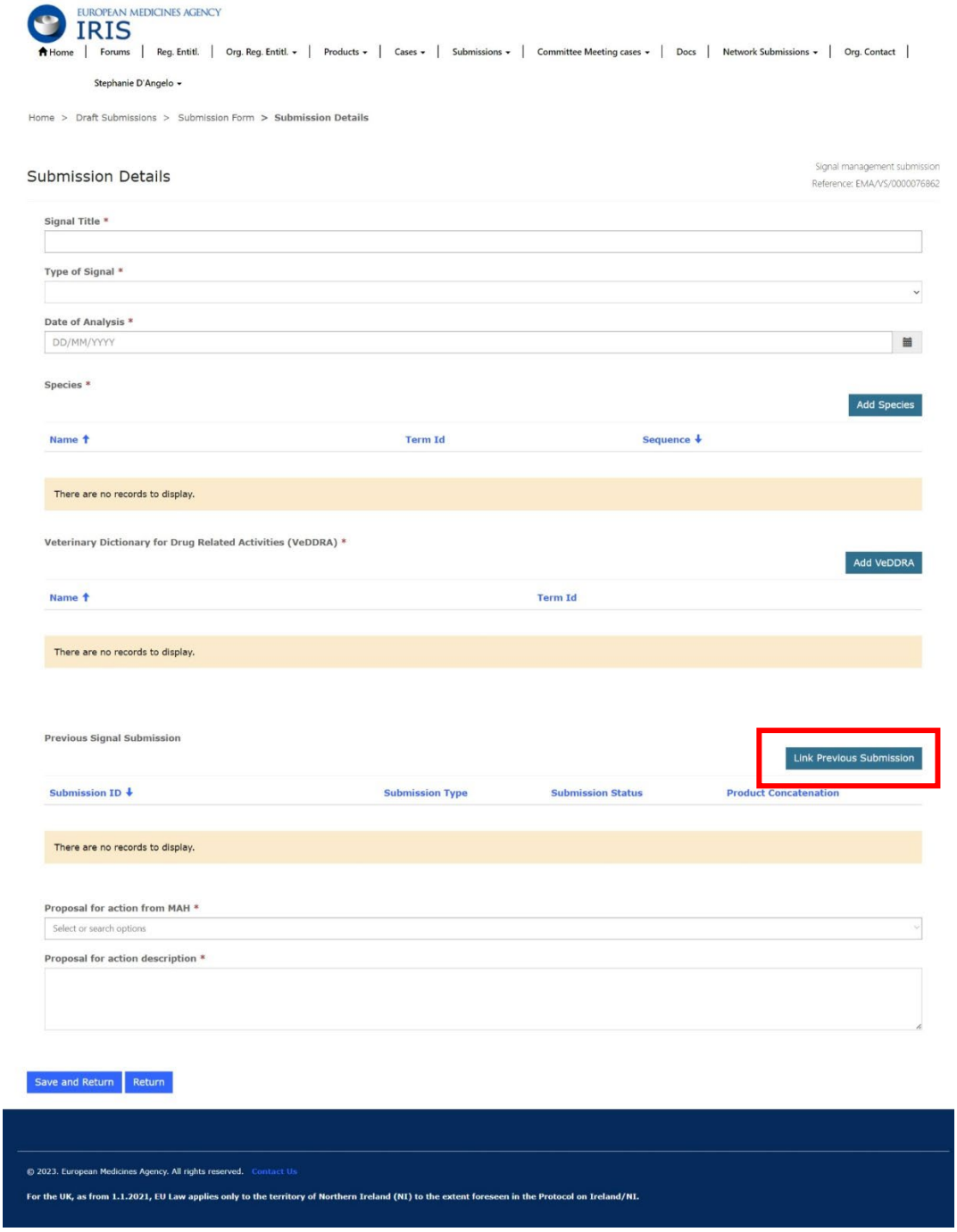
*Screenshot: The function to link signal submissions is found under "Submission Details", see red box.*




*Screenshot: Signal submissions are linked using the "Link Previous Submission" function, see red box.*