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Veterinary Medicines Division

# EudraVigilance Veterinary – Best practice guide

## Contents

# Introduction

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: https://www.ema.europa.eu/en/documents/other/evvet-evweb-user-manual_en.pdf, https://www.ema.europa.eu/en/documents/scientific-guideline/eu-vich-adverse-event-report-implementation-guide_en.pdf, https://www.ema.europa.eu/en/veterinary-regulatory/post-authorisation/pharmacovigilance/guidance/veterinary-international-conference-harmonization-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 2.7.).

# 1. Administrative and identification information

## 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 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 https://vichsec.org/en/guidelines/pharmacovigilance/vich-gl30.html, 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):
https://www.vichsec.org/en/guidelines/pharmacovigilance/vich-gl30.html

| 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.**

## 1.2. "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 2.3). For environmental incidents, the value "Other" should be selected (see also section 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.

## 1.3. 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" (see also section 1.2),

- The 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:*

Type of Information in Report

OTHER

AER Term Name *

Environmental adverse event ⊗

*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).

## 1.4. 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, concatenated, 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:**

Primary Reporter Information ⑦

⬤ Withhold

First name

Last name *
GS12

Telephone

## 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 category of 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 elements fields nor in the case narrative:

- 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 5 of this document.

# 2.  Description of the AE

## 2.1.  How to record animal/human data

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

Enter the numbers of animals or humans treated, or 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 treated (exposed) human(s) (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 the 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 <u>treated</u> animals should be provided.

If the number of animals affected is not known, the estimated number of <u>affected</u> 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 human 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 human 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.

### Animal/Human Data ⑦

Number of Animals Treated
1

Number of Animals Affected *
1

Attending Veterinarian's Assessment of Health Status Prior to VMP

Species (Type of Species) *
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.

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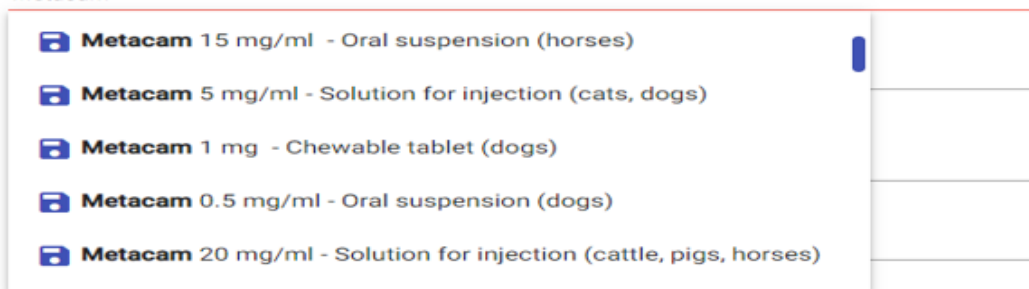
The Union Product Database (UPD) is the source of this information in EVV for veterinary medicinal products. Information related to non-medicinal products (e.g., food supplements, biocides) should only be included in the case narrative.

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.

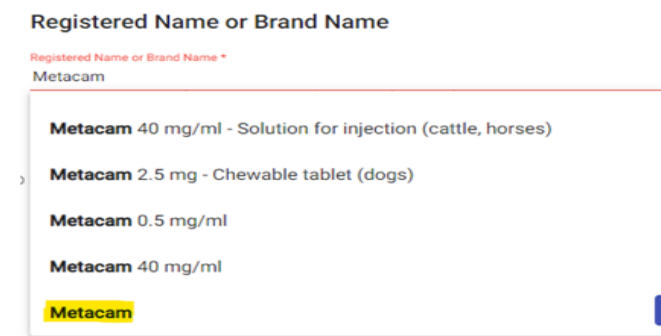When the registered name or brand name (B.2.1) is not known, **the active substance name** should be recorded in the field "Active ingredient(s)" (B.2.2.1) in the section "Active Ingredient(s)" (B.2.2).

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:*
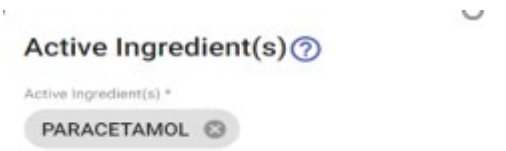
1.



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 products, 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 AE 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 the 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:*
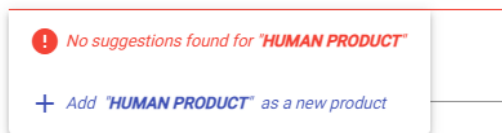


The route of administration (Route of exposure) (B.2.1.7), dose (Dose per administration) and interval of administration treatment should be recorded. These data facilitate the assessment on whether the product was used outside the terms of the marketing authorisation.

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:*

**Route of exposure**

Route of Exposure (Route of Administration)
ORAL

**Dose Per Administration** ⑦

Numeric Value for Dose (Numerator)
1

Units of Value for Dose (Numerator) ⑦

| Units of Measurement | | Units of Presentation |
| --- | --- | --- |
| | | tablet |

Numeric Value for Dose (Denominator)

Units Value for Dose (Denominator) ⑦

| Units of Measurement | Units of Presentation | Dose denominator qualifiers |
| --- | --- | --- |

Numeric Value for Interval of Administration
1

Units of Value for the Interval of Administration *
Month

| Choose a Date Format | Date of First Exposure |
| --- | --- |
| Day, Month and Year | 2022/01/01 |

| Choose a Date Format | Date of Last Exposure |
| --- | --- |
| Day, Month and Year | 2023/02/01 |

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:*

**Route of exposure**

Route of Exposure (Route of Administration)
INTRAVENOUS

**Dose Per Administration** ⑦

Numeric Value for Dose (Numerator)
10

Units of Value for Dose (Numerator) ⑦

| Units of Measurement | | Units of Presentation |
| --- | --- | --- |
| Milligram | | |

Numeric Value for Dose (Denominator)
1

Units Value for Dose (Denominator) ⑦

| Units of Measurement | Units of Presentation | Dose denominator qualifiers |
| --- | --- | --- |
| Milliliter | | |

Numeric Value for Interval of Administration

Units of Value for the Interval of Administration

| Choose a Date Format | Date of First Exposure |
| --- | --- |
| Day, Month and Year | 2023/02/01 |

| Choose a Date Format | Date of Last Exposure |
| --- | --- |
| Day, Month and Year | 2023/02/01 |

Previous Exposure to the VMP

Previous Exposure to the VMP                                                   ◉ Yes  ○ No  ○ Unknown  ?

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.

## 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). Additional medicinal products mentioned by the primary source can be recorded in the above-mentioned fields 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 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.

## 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.

## 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 1.2).

*Type of information in Report:*

Type of Information in Report
BOTH SAFETY AND LACK OF EXPECTED EFFECTIVENESS

*AER Term Name:*

Lack of efficacy (parvovirus)

Lack of efficacy (myxomatosis)

Lack of efficacy (tick)

Partial lack of efficacy

Lack of efficacy (fly)

AER Term Name *
lack of e    🔍   ⑦

This field is required

*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 1.2).

 **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:

**Vaccine L4 (AEs)**
- Transient increase body temperature
- Small transient swelling
- Anaphylaxis

**Leptospirosis signs**
- Bleeding
- Hepatitis
- Jaundice
- Nephritis

Vaccine L4 – Bleeding → drug-event pair
Vaccine L4 – Hepatitis → drug-event pair
Vaccine L4 – Jaundice → drug-event pair
Vaccine L4 – Nephritis → drug-event pair

Product X – Hepatitis

$$ROR = \frac{p_1}{p_0} = \frac{\text{Reports with Product X with and without hepatitis}}{\text{Reports with other products with and without hepatitis}} \longrightarrow = \frac{p_1}{p_0 \Uparrow} = ROR \Downarrow$$

Vaccine L4 – Hepatitis → drug-event pair

<u>Correct and incorrect coding approach:</u>

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.

**Case 1 (Product X)**
**Safety issue report**
VeDDRA terms reported:
- Hepatitis ✓

Type of Information in Report

LACK OF EXPECTED EFFECTIVENESS
BOTH SAFETY AND LACK OF EXPECTED EFFECTIVENESS
SAFETY ISSUE
OTHER

**Case 2 (Vaccine L4)**
**Lack of efficacy report**
VeDDRA terms reported:
- LEE
- Hepatitis ✗

Type of Information in Report

LACK OF EXPECTED EFFECTIVENESS
BOTH SAFETY AND LACK OF EXPECTED EFFECTIVENESS
SAFETY ISSUE
OTHER

**Case 3 (Product Y)**
**Both safety and lack of expected effectiveness**
VeDDRA terms reported:
- LEE
- Hepatitis ✓

Type of Information in Report

LACK OF EXPECTED EFFECTIVENESS
BOTH SAFETY AND LACK OF EXPECTED EFFECTIVENESS
SAFETY ISSUE
OTHER

## 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 http://www.emea.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500005087.pdf).

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:_

AER Term Name *

Death ✕    🔍   ⑦    Number of Animals: 5

AER Term Name *

Death by euthanasia ✕    🔍   ⑦    Number of Animals: 1

Outcome to Date ⑦

Ongoing

Recovered / Normal

Recovered with Sequela

Died
5

Euthanized
1

Unknown

## 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".



## 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.

## 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.).

Number of Animals Treated

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

Number of Animals Affected *

This field is required

- 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 reduce 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/reduce 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** | Parents +/- offspring | Parents. Offspring is not counted. | offspring |
| 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.

# 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. Sender organisations should endeavour to search EVV prior to recording an AER, in order to prevent duplicates occurring.

The process for handling of duplicate reports 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 is not yet available. Until further notice, please follow the process described below.

Each organisation, whether MAH or NCA, that has received a report on a suspected adverse event should check EVV before submitting an AER.

Each organisation, whether MAH or NCA, that has received a report on a suspected adverse event and becomes aware that it is a duplicate of an AER already recorded in EVV by another organisation before they send 'their' AE to EVV, should not send their own report with a different AERID to EVV. Instead, they should contact the sender organisation of the initial report if they have significant new

information. The initial sender organisation should then send a follow-up (see section 5 for further information) to the existing AER in EVV (please see notice above regarding temporary suspension of follow-up reports by organisations other than the initial sender organisation).

When a suspected duplicate AER is detected, the following procedure should be followed:

The AERs need to be compared thoroughly to establish the similarities and differences in the data entry between the AERs. There are two possible outcomes:

1) AERs, although similar, are not duplicates -> nothing to be done,

2) AERs are confirmed to be duplicates, in which case carry out the following steps:

- The organisation identifying the suspect duplicate AER contacts the other organisation(s) involved.

- Establish agreement between all parties involved to determine which AER is retained & which is to be nullified. If an NCA is involved, the NCA decides which AER is retained & which is to be nullified and who updates the AER.

- The retained AER should be updated with any additional information from the AER(s) to be nullified.

- The AERID of the AER retained should be communicated to all parties -> any subsequent follow-up reports are recorded in EVV using the correct AERID.

- The AERs considered as duplicate are nullified by the original sender organisation(s) (see also section 4. for nullification).

# 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).
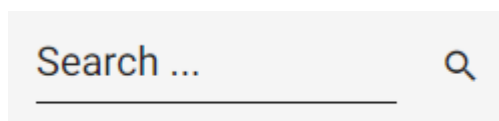


The AER may also be retrieved by searching in the "Search AE Reports" section by entering the AERID in the criteria section (see below).
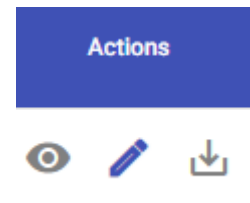
Once the AER is retrieved, the "Follow-up/Nullification" icon should be selected in the "Action" section (see below) in order to transfer the AER to the "Create and Send" section.



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).
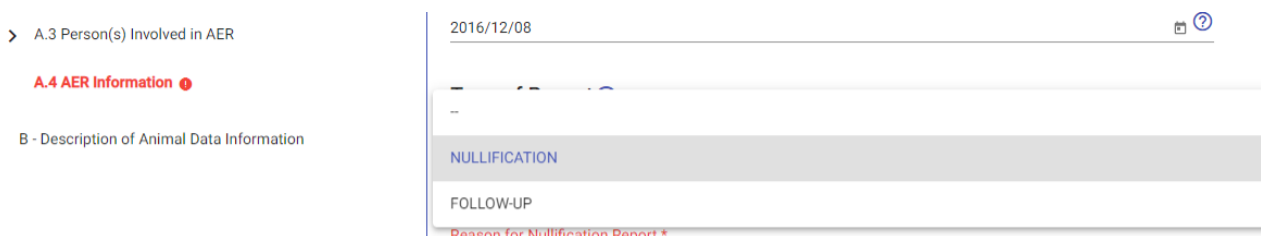


Once "NULLIFICATION" is selected, the field "Reason for Nullification Report" should be completed with the information on the reason for the nullification (see below).

**A.4 AER Information** 🔴

B - Description of Animal Data Information

**Type of Report** ❓

Type of Submission *

NULLIFICATION

Reason for Nullification Report *

This field is required

The nullification report can now be recorded in EVV.

# 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 the 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 exemplified 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.<br><br>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. | Follow-up AER recorded in EVV.<br><br>**NB:** Information that has been added should be stated clearly in the case narrative. |
| Non-significant information | Changes that do not impact the evaluation or | Changes of VeDDRA terms within same PT (unless a clear and significant difference). | **NO** follow-up AER recorded in EVV. |

| | recording of the AER in EVV. | 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. | 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". |

# 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".