EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

VGVP module on collection and recording of suspected adverse events for veterinary medicinal products & EVV system functionalities

Veterinary Risk and Surveillance
Veterinary Medicines Division

Webinar training
10 November 2021

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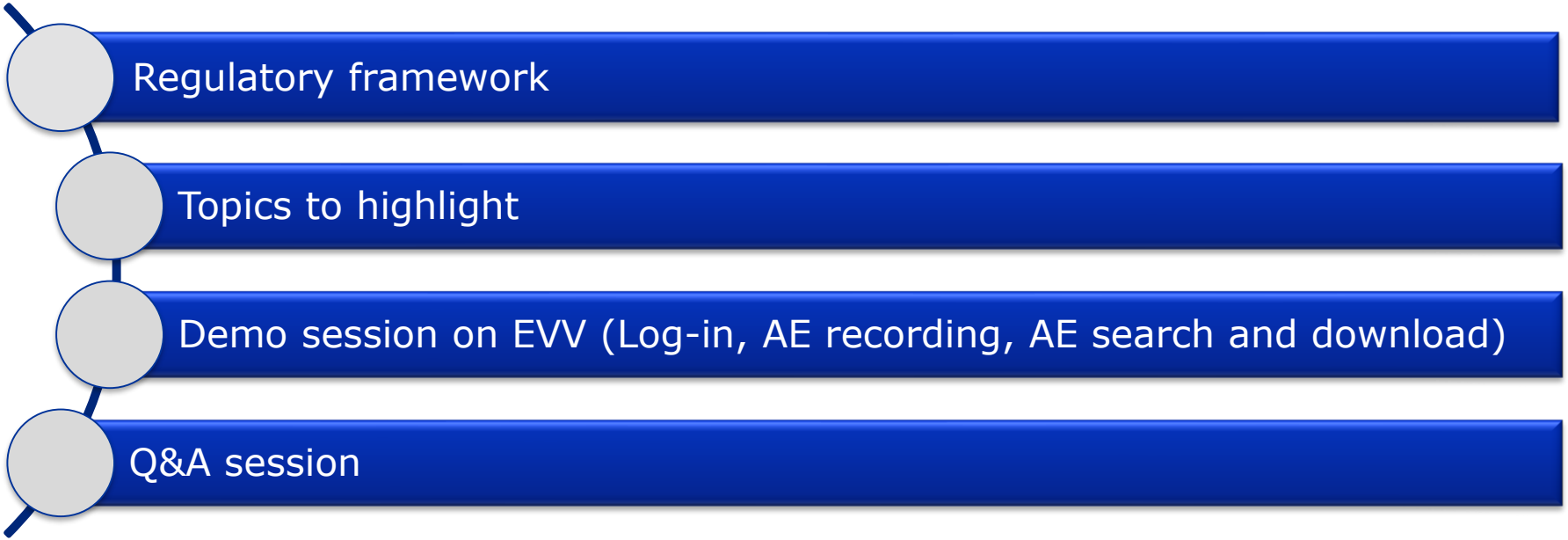
Note:

This training is focused on the new elements for the collection and recording of suspected adverse events for veterinary medicinal products in accordance with Regulation (EU) 2019/6.

Step-by-step tutorials focused on the use of EVV will become available shortly.

Content Summary



Regulatory Framework

EU Veterinary Medicines Legislation

- Regulation (EU) 2019/06
- Commission Implementing Regulation (EU) 2021/1281
- VICH Guidelines 24, 30, 35 & 42

Regulation (EU) 2019/6 Article 73(2)

Competent authorities, the Agency and marketing authorisation holders shall take the necessary measures to make available means to report and encourage reporting of the following suspected adverse events:

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

Regulation (EU) 2019/6 **vs** Volume 9B - Main differences for AER collection and recording (1/2)

- All suspected adverse event reports (AERs) should be recorded directly in EVV;
- Timeframe for all AERs recording in EVV: 30 calendar days;
- No difference between serious and non-serious adverse events for reporting obligations and signal detection, however the field "Serious AE" is mandatory in EVV (Yes, No);
- Requirement for collection and recording of any observation of a lack of efficacy of a veterinary medicinal product (VMP) following its administration to an animal, whether or not in accordance with the summary of product characteristics;

Regulation (EU) 2019/6 **vs** Volume 9B - Main differences for AER collection and recording (2/2)

- Requirement for collection and recording of environmental incidents (NEW DEFINITION);
- Requirement for collection and recording of any unfavourable and unintended reaction in an animal to a medicinal product for human use;
- No causality assessment required at individual case report level;
- AERs originating from clinical studies for authorised VMPs & post-marketing surveillance studies for VMPs should be recorded in EVV within 30 days from the date of the closure of the final study report.

Topics to highlight

Serious adverse event (AE) classification

The field is mandatory in the reporting form. In the absence of a definition of seriousness in the new EU regulation, the decision on the AE seriousness classification in EVV (i.e. serious vs non-serious) should follow the VICH definition of a "serious adverse event" (see VICH GL24):

"A serious adverse event is any adverse event which results in death, is life-threatening, results in persistent or significant disability/incapacity, or a congenital anomaly or birth defect. For animals managed and treated as a group, only an increased incidence of serious adverse events as defined above exceeding the rates normally expected in that particular group is considered a serious adverse event".

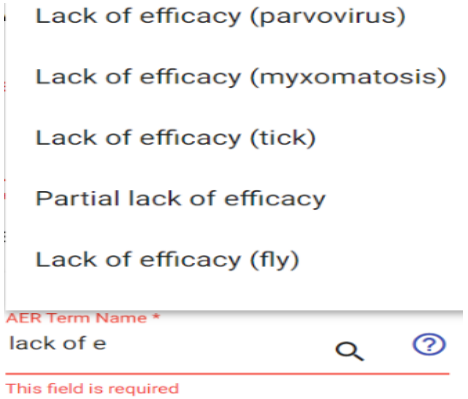
Example from EVV:

Lack of expected effectiveness (LEE)

It is now possible in EVV to record cases which have both safety and lack of expected effectiveness elements, by selecting the following entry in the "Type of Information in Report" field: "**Both safety and lack of expected effectiveness**".

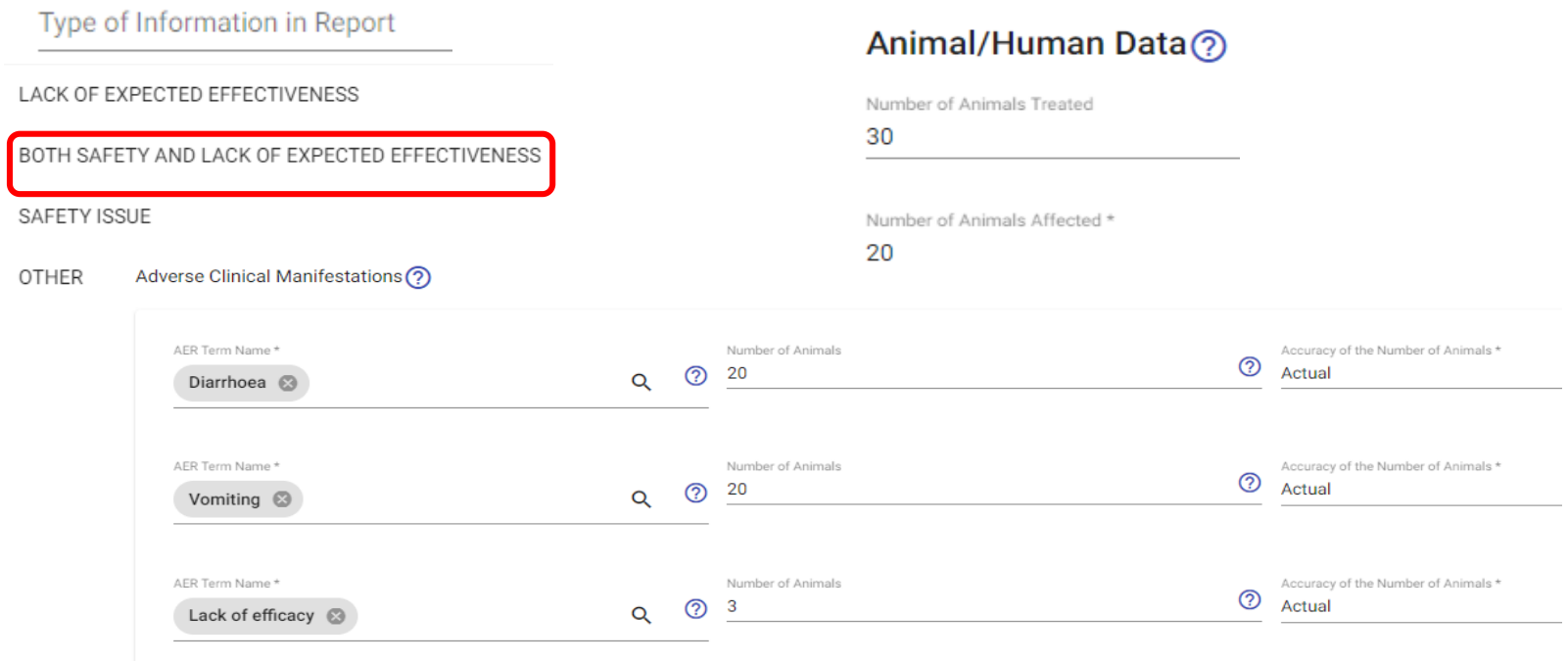
All the relevant VeDDRA terms (both for lack of efficacy and for safety) should be selected according to the document "Guidance notes on the use of VeDDRA terminology for reporting suspected adverse reactions in animals and humans".

Example from EVV:



Lack of expected effectiveness (LEE)

Example: 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.



LEE: Considerations (not new, but of high importance)

Signs of the disease should not be coded as VeDDRA terms.

Example

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

LEE: Considerations (not new, but of high importance)

The VeDDRA terms for the disease signs may appear as new signals and may mask potential signals for other products.

Example of signal masking:

Product X – Hepatitis

$$ROR = \frac{p_1}{p_0} = \frac{\text{Reports with Product X with and without hepatitis}}{\text{Reports with other products with and without hepatitis}} = \frac{p_1}{p_0 \uparrow\uparrow} = ROR \downarrow\downarrow$$

Vaccine L4 – Hepatitis → drug-event pair

Recording of LEE in EVV (not new, but of high importance)

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

Environmental incidents – Definition and recording in EVV

Definition of environmental incident:

A situation where an ecosystem is adversely affected through exposure to a veterinary medicinal product, its active substance(s) or its metabolites present in different environmental compartments (e.g. soil, water) or animal remains. Such incidents may consist of, for example, presence of the active substances in soil or water or wildlife poisoning by a substance to levels considered harmful for the ecosystem affected. Events related to user safety are not considered environmental incidents.

- The type of information in the suspected adverse event report should be "Other" and the relevant VeDDRA term(s) should be selected. Any specific information regarding environmental incidents should be recorded in the case narrative.

Example from EVV:

Environmental incidents - Recording in EVV

Example of AER

Case narrative: In DD/MM/YYYY a sheep owner dipped his sheep in a 5000 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

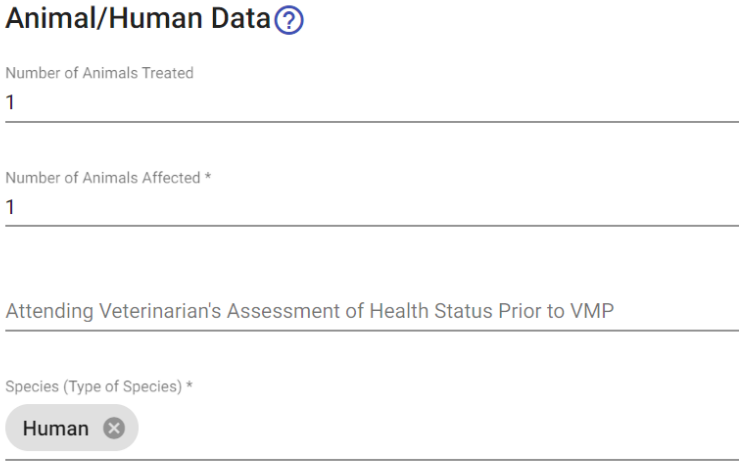
The number of ***affected*** animals should be the number of fish (**mandatory**)
The Species should be fish (i.e. Affected species)
Note: The number of *treated* animals should be the number of sheep (**not mandatory**)

Cases of adverse reactions in humans exposed to VMPs

Unlike in DEG (EVVET2), in VICH there is no separate form to record AERs in humans:

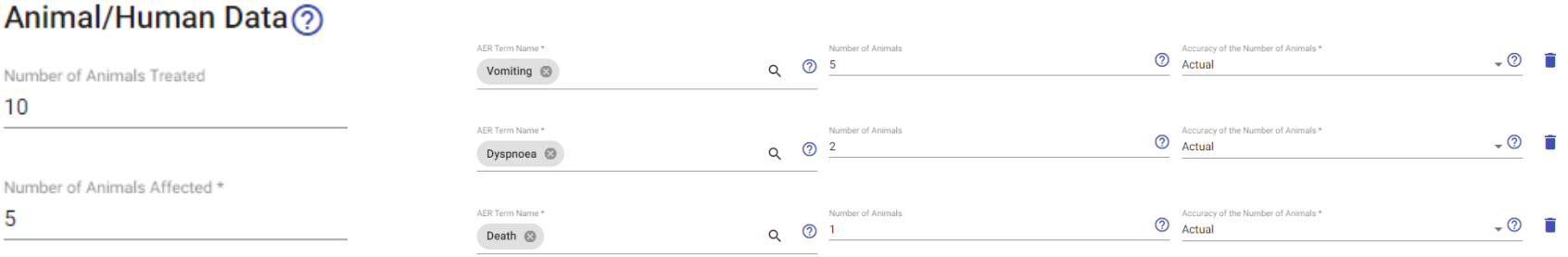
- "Human" is selected as a "species".
- Only one human affected per AER. If more than 1 human is affected, another AER should be created and the AERs should be linked.

Example from EVV:



VeDDRA terms recording in EVV

The number of animals affected should be recorded in EVV against each VeDDRA term as well as in the "Number of animals affected" field.

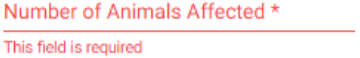


What to do if precise information is not available: Record the number as "estimated".

Suspected AERs for offspring exposed through a parent

- The number of animals ***treated*** should ALWAYS be the parent.

- The number of animals ***affected*** should be recorded in the relevant mandatory field as well as against each relevant VeDDRA term, as per general rule for all AERs.



Suspected AERs for offspring exposed through a parent

- The treatment start date should be the date the parent was treated.

- The clinical signs in the case narrative should include the clinical signs of the offspring as well as of the parent.

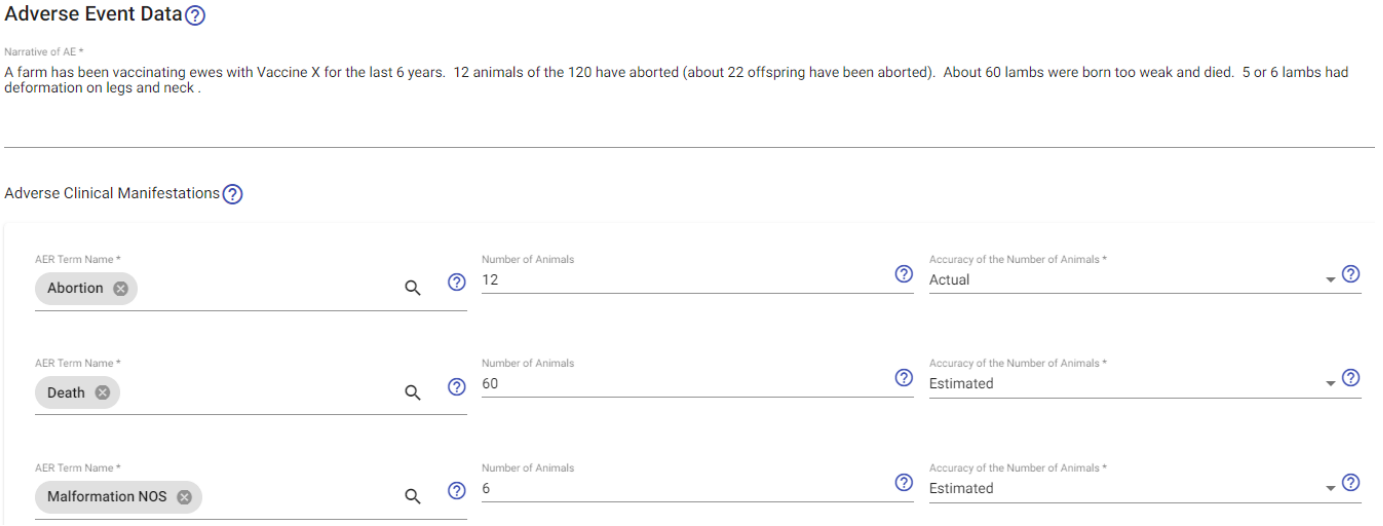
- Record number of parent + offspring in "number of animals affected"

  Abortion: Record number of the parent only as number of animals affected and against the VeDDRA term "abortion".

  Stillbirth: Record the number of dead offspring as number of animals died and against the VeDDRA term "stillbirth".

Suspected AERs for offspring exposed through a parent

Examples



Comment: The number 12 reflects the number of parent(s). Additionally, the number of aborted offspring should be stated in the case narrative if available.

Suspected medicinal products/active substances identification

All medicinal product(s)/active substance(s) included in an AER recorded in EVV will be considered **suspected** during the process of signal management.

It is recommended to record in the case narrative the opinion of the primary reporter identifying which medicinal product(s)/active substance(s) are considered suspected, when available.

The available field in the VICH guideline on pharmacovigilance VICH GL42: "B.5.1. Attending veterinarian's assessment" can only capture this type of information at report level, without indicating the actual products, and therefore this field can be left blank.

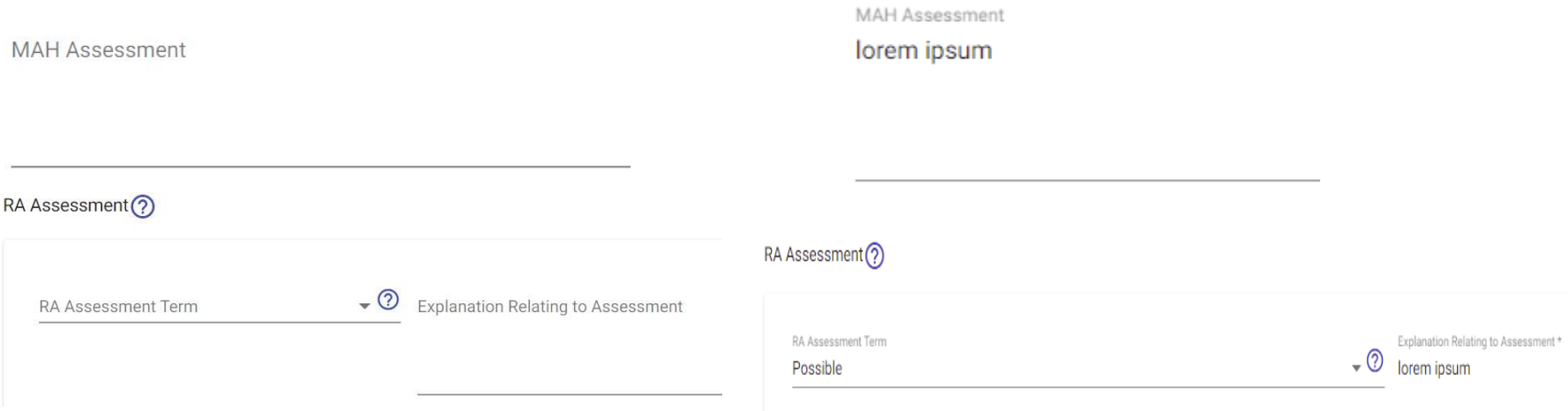
The available fields foreseen by VICH to collect this information (see VICH GL42: "B.2.1.5. MAH assessment", "B.2.1.6. RA assessment"), can therefore be left blank.

Marketing Authorisation Holder (MAH)/National Competent Authority (NCA) assessment

The MAH/RA assessment can be left blank.

Note: AERs e.g. 3rd country reports with MAH/RA assessments, will continue to be accepted.

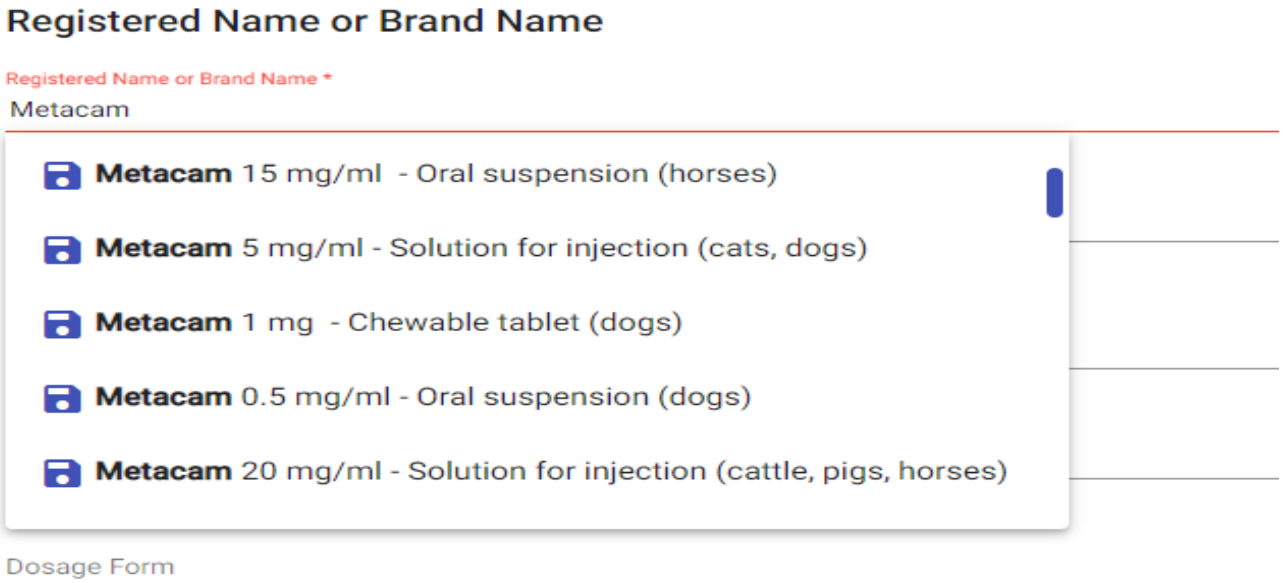
Example from EVV:



How to record a VMP included in the Product Dictionary (UPD)

When recording the product name, it is advisable to select an entry marked with the symbol , if possible. This will ensure that the product mentioned in the AER is automatically linked with the UPD, which is crucial for L2 access to the case, and for allowing grouping of data for signal detection.

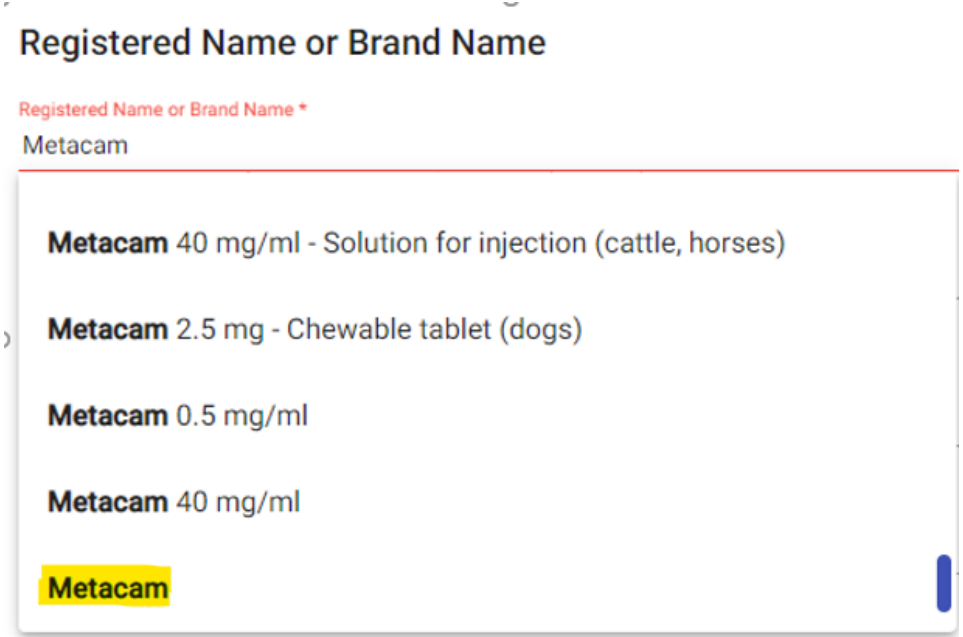
Example from EVV:



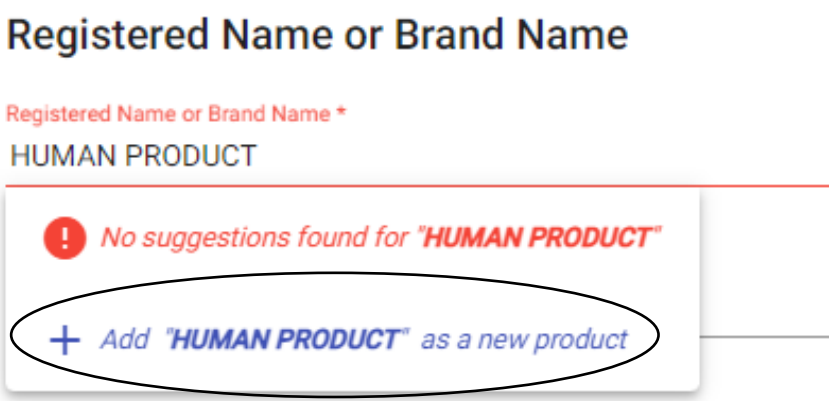
How to record a medicinal product when only partial information is available

When recording the product name, it is possible to select the entry according to the information available. Thus if only the "Invented name" is known, while not the strength or pharmaceutical form, it is possible to select an entry to reflect the information available.

Example from EVV:



How to record a medicinal product not included in the Product Dictionary (UPD) (e.g. medicinal product for human use)



After searching for a product that is not included in the Product Dictionary, the product can be recorded manually in EVV by clicking on “Add “Product X” as a new product”.

Suspected AERs where only the active substance is known

- These AERs should be recorded in EVV
- The system business rules accept AERs where only an active substance is recorded (i.e. no brand name is recorded)
- This also applies when for the concomitant product(s) only the active substance(s) is/are known

Example from EVV:

1. **Registered Name or Brand Name**

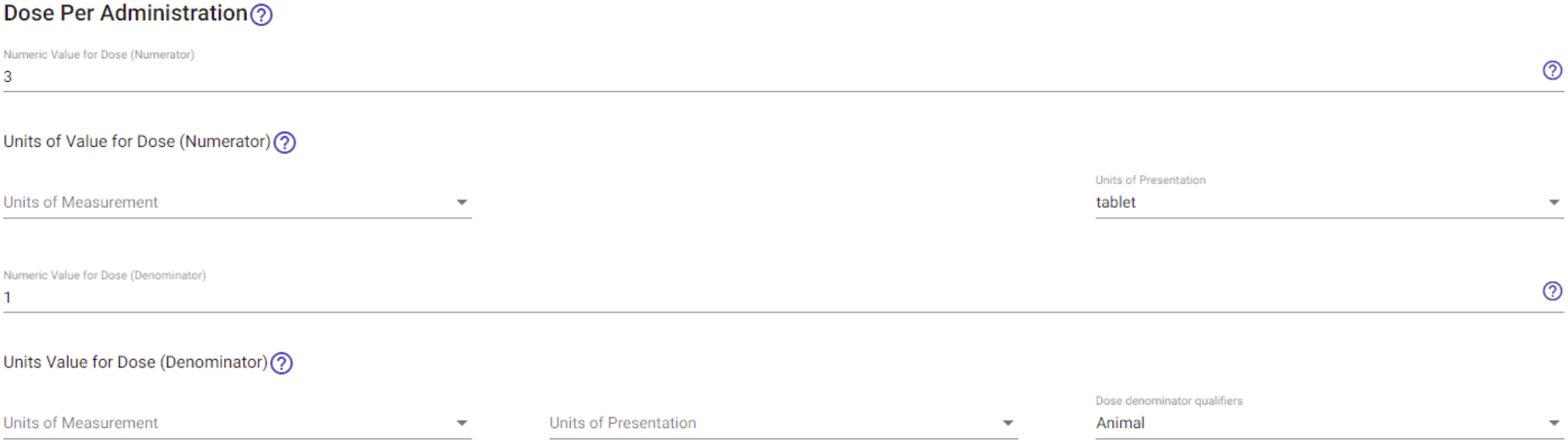
2.

3 **Registered Name or Brand Name**

How to record dosage information in EVV (1/2)

Example from EVV:

The owners give 3 tablets to their dog.
Numeric value numerator 3
Unit for numeric value numerator tablets
Numeric value denominator 1
Unit for numeric value denominator animal

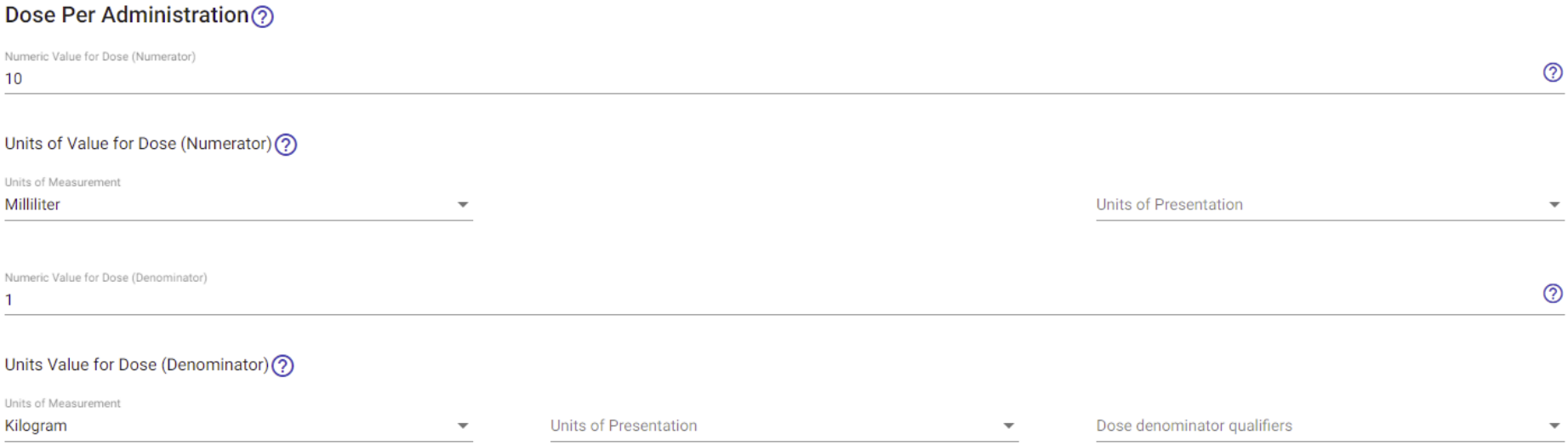


How to record dosage information in EVV (2/2)

Example from EVV:

The veterinarian gives each animal in the herd 10 ml of the VMP per kg of body weight.

Numeric value numerator 10
Unit for numeric value numerator ml
Numeric value denominator 1
Unit for numeric value denominator kg

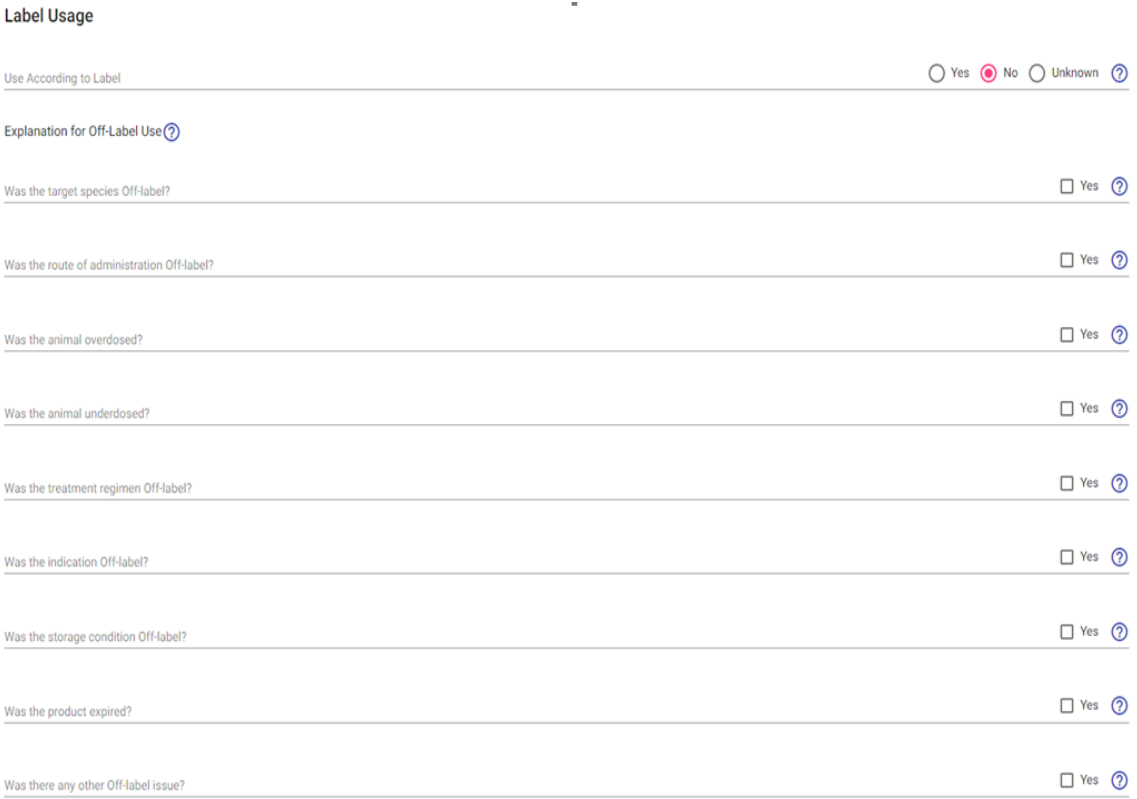


Off-label use: How to record off-label use in EVV

Examples (1/2)

- A sheep is treated with 3 mg/kg ketoprofen IM SID for 3 days. The product is authorised for the target species cattle, horse, pig -> Target species: Off-label.

- Cat received 20 µg/kg buprenorphine SC. According to the SPC the product is approved for IV or IM administration -> Route of administration: Off-label.



Off-label use : How to record off-label use in EVV

Examples (2/2)

Products used in combination:

Ketamine product for the induction of anaesthesia in dogs. Substances allowed for use in combination according to the SPC: medetomidine, xylazine, diazepam.

Combination with any other substance (e.g. opioids for additional analgesia) is off-label use (treatment regimen).

Different dose recommendations in the SPCs of the substances used in combination:

- e.g. Ketamine product (40 µg/kg medetomidine + 5 – 7.5 mg/kg ketamine) vs. medetomidine product (80 µg/kg medetomidine + 2.5 mg/kg ketamine)
- If the veterinarian follows the recommendation of the medetomidine product, the use is off-label (underdosed) for the ketamine product

In veterinary practice anaesthetics are often given to effect – this may also result in off-label use (overdose/underdose) when compared to the dose recommendation as provided in the SPC.

Unique Adverse Event Report Identification Number (AERID)

Regulatory Authority (RA)

- Country of occurrence can only be stated in 1st part of the Unique Adverse Event Report ID Number (AERID). No separate field is available on VICH format.

- The value should follow the format below:

Country of occurrence code (3 digits)–VICH RA Identifier code (8 digits)–Internal case reference code

Example for Danish Agency:
DNK–DNKMEDAG-12345678

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

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

Unique Adverse Event Report Identification Number (AERID)

Marketing Authorisation Holder (MAH)

- Country of occurrence: Same rule as for NCA
- The MAH AERID should follow the format below:

Country of occurrence code (3 digits)-MAHORGID (8 digits)–ROUTINGID + remaining text (up to 47 digits)

MAHs currently registered in EVVET, with an existing Routing(sender) ID that is longer or shorter than 8 digits (and they have not yet been provided a 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 CAPS. The MAHORID and the Routing(sender) ID obtained should be used for all AERs.

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

Further guidance is provided in the EVV Best practice guide.

Adverse Event Report (AER): Initial **vs** Follow-up

The AERID from the initial AER should NOT be changed when recording a follow-up AER.

Initial AER

- Original receive date = Date of receipt of **initial** info from primary source
- Type of report: Initial

Allows calculation of 30 day compliance (calculated from "Message received date").

Follow-up AER

- Original receive date should not be changed when recording follow-up reports
- Type of report: Follow-up

Date of current submission (Most recent info date) for Initial AERs and Follow-up AERs: Under discussion.

Duplicate management

MAHs and NCAs can follow-up on other Sender's AERs.

Interim practice until duplicate management system is established:

When a suspect duplicate is detected -> Compare AERs -> Two possible outcomes:
1) AERs, although similar, are not duplicates -> Nothing to be done
2) AERs are confirmed to be duplicates -> Steps to be followed:
- The organisation identifying the suspect duplicate AER, contacts the other organisation(s).
- Agreement between all parties involved to determine which AER is retained & which is/are to be nullified.
- AER retained should be updated with any additional information from the AER(s) to be nullified.

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

The sender organisation(s) nullifies(y) the AERs deemed as duplicate(s).

If various versions of a duplicate report exist in EVV (e.g. an initial and follow-up AERs) -> **Sender of the latest follow-up should send the nullification.**

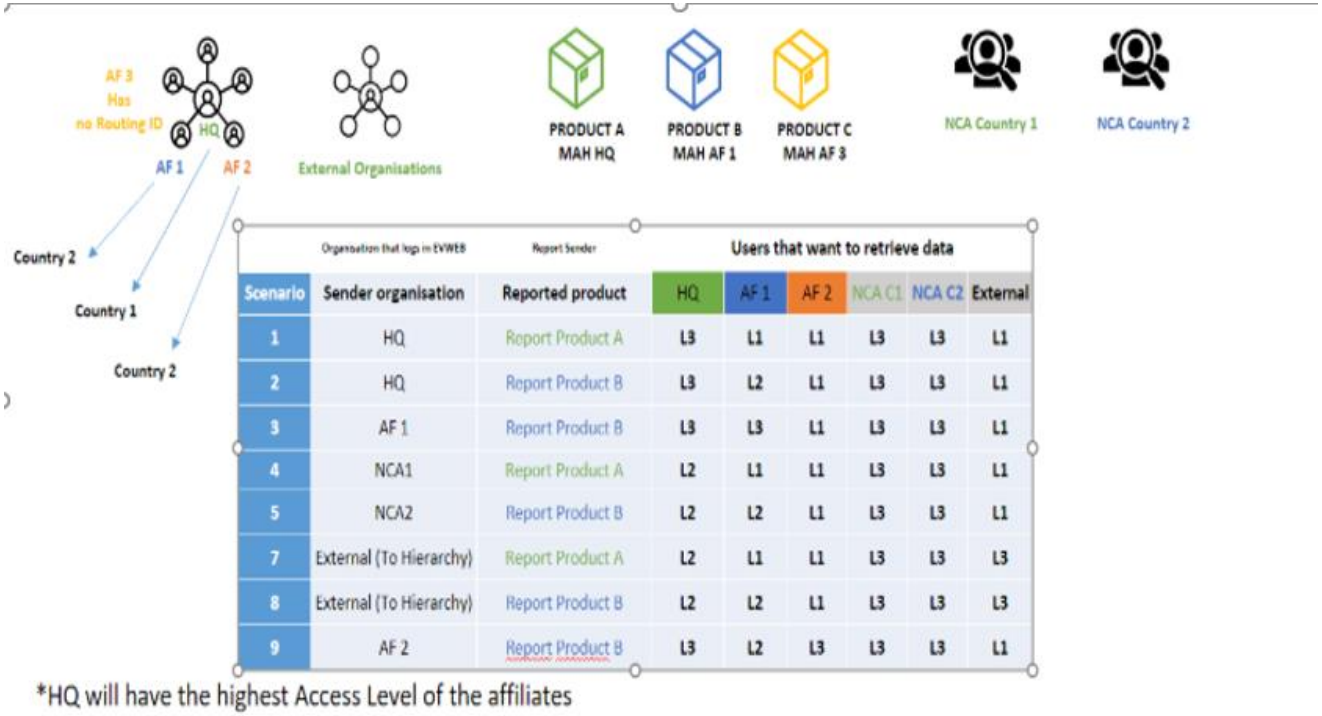
EVV access policy

- Access to AERs sent by MAH (Level 3: as previously)
- Access to AERs for MAH products sent by other organisations (Level 2: Includes case narrative) NEW
- Access to all other AERs (Level 1: Same as public reports) NEW

Link to Access Policy for EVV:
https://www.ema.europa.eu/en/documents/scientific-guideline/eudravigilance-access-policy-medicines-veterinary-use-revision-2_en.pdf

MAHs–Access to AERs

Scenarios for HQs / Affiliates



	Organisation that logs in EVWEB	Report Sender	Users that want to retrieve data					
Scenario	Sender organisation	Reported product	HQ	AF 1	AF 2	NCA C1	NCA C2	External
1	HQ	Report Product A	L3	L1	L1	L3	L3	L1
2	HQ	Report Product B	L3	L2	L1	L3	L3	L1
3	AF 1	Report Product B	L3	L3	L1	L3	L3	L1
4	NCA1	Report Product A	L2	L1	L1	L3	L3	L1
5	NCA2	Report Product B	L2	L2	L1	L3	L3	L1
7	External (To Hierarchy)	Report Product A	L2	L1	L1	L3	L3	L3
8	External (To Hierarchy)	Report Product B	L2	L2	L1	L3	L3	L3
9	AF 2	Report Product B	L3	L2	L3	L3	L3	L1

*HQ will have the highest Access Level of the affiliates

Any questions?

Further information

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