10 October 2013
EMA/CVMP/PhVWP/552/2003 – Rev.1
Committee for Medicinal Products for Veterinary Use (CVMP)

Recommendation on harmonising the approach to causality assessment for adverse events to veterinary medicinal products

Adoption of guideline by CVMP	15 April 2004
Draft recommendation agreed by the PhVWP-V	January 2013
Draft recommendation adopted by CVMP for release for consultation	7 February 2013
End of consultation (deadline for comments)	31 May 2013
Agreed by PhVWP-V	September 2013
Adopted by CVMP	10 October 2013
Date for coming into effect	1 January 2014

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Executive summary

This recommendation provides further guidance on how to carry out causality assessment, based on the principles laid out in Volume 9B of The Rules Governing Medicinal Products in the European Union (EU) – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use and includes additional guidance on causality assessment of adverse events classified as off-label and lack of expected efficacy (LEE) concerning pharmaceuticals. For vaccines guidance on LEE reports and adverse events after mixing of vaccines will be provided in due time.

1. Introduction (background)

The guideline on harmonising the approach to causality assessment for adverse reactions to veterinary medicinal products (EMEA/CVMP/552/03) that came into effect on 15 October 2004 has been revised and renamed as a 'recommendation'.

The aim of this recommendation is to provide a basis for a common understanding and uniform approach to performing causality assessment for adverse events to veterinary medicinal products (VMPs), using the ABON-system outlined in Volume 9B. According to this system, five categories of causality can be selected (A = probable; B = possible; O1 = inconclusive; O = unclassifiable/unassessable; and N= unlikely to be product related (not related, as there is information available that proves that the adverse event is not related to the VMP)).

According to EU guidance (see Volume 9B) competent authorities as well as marketing authorisation holders (MAHs) are required to perform causality assessment. The practises for assessing causality currently appear to differ within and between Member States' competent authorities and MAHs. To improve data quality and effectiveness of the pharmacovigilance system it is necessary to ensure consistency of causality coding performed by competent authorities as well as the veterinary pharmaceutical industry.

It is acknowledged that an algorithm may be a useful tool to achieve consistency in causality assessment, provided that there is an option available for experienced expert judgement to override the algorithm coding when necessary. However, no algorithm or decision tree for automated causality assessment is proposed at this point in time. It is proposed that this recommendation be revisited at a later point of time to address concepts which require more in-depth consideration such as the principle of causality assessment within the process for surveillance of data contained in EudraVigilance Veterinary (EVVet). Additionally the guidance should address the use of an algorithm for causality assessment, the issue of causality assessment of lack of expected efficacy (LEE) reports for immunologicals and adverse events occurring after mixing of vaccines.

2. Scope

A need for better harmonisation of criteria for analysis and assessment of reported adverse events to VMPs has been identified. To ensure consistency in coding using the ABON-system within and between pharmacovigilance personnel in competent authorities as well as in industry, common approaches to analysing, assessing and coding of reported adverse events will be set.

This is particularly important with regard to the implementation of electronic reporting of adverse events to veterinary medicines through EVVet. While the ABON codes are allocated to individual reports after assessment, the database in EVVet will for the first time make accessible at one point all expedited adverse events reported to the EU Member States, whether classified A, B, O1, O or N.

Analysing events across all codes would reduce bias introduced when allocating the codes. This is particularly important for detecting events due to unexpected and/or unknown pharmacological and/or immunological properties.

Six main factors should be taken into account: associative connection, pharmacological and/or immunological explanation, clinical or pathological phenomena, previous knowledge, other causes and reliability of data. In a questionnaire this recommendation compiles guiding questions for each aspect, which are meant as examples and not intended to be exhaustive. They facilitate finding the answer to the main and conclusive question, which is listed at the end of each section. Within the first four factors "yes"-answers to the conclusive questions point towards A and B codings, whereas for the last two factors "yes" answers point away from A.

With respect to causality assessment, no distinction is made between products administered in accordance with the recommendations of the summary of product characteristics (SPC) and those used off-label (unauthorised target species, unauthorised route of administration, given in overdose, etc.). Causality assessment takes into consideration both product and treatment, whereas regulatory actions will generally be triggered by product related causality.

3. Legal basis

The basis for this recommendation is the current EU legislation concerning pharmacovigilance activities on nationally and centrally authorised veterinary medicinal products, which is further outlined in Volume 9B – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use (see section 8. References).

4. Questionnaire

4.1. Associative connection

a. in time (including de-challenge and re-challenge)

b. with anatomical site.

4.1.1.

Is the observed event associated with the administration of the VMP? Is the chronology in good accordance with treatment? Is there a reasonable association in time between the administration of the product and the onset and duration of the adverse event?

- Is there a reasonable association in time between the administration of the product and the onset of the adverse event?

yes	no	not known
reasonable association	no reasonable association	unknown
A, B	**N**	**O1 or O**

4.1.2.

- Has there been any improvement after stopping treatment or giving an antidote (de-challenge)?

yes	no	not known
improvement	no improvement	no de-challenge done
A, B	**O, N**	**A, B, O1, O, N**

4.1.3.

Did the adverse event reappear after re-challenge (same or related animal)? Is a similar event known in that patient from previous exposure?

- What happened after re-challenge - recurrence, no recurrence or no re-challenge done?

yes	no	not known
recurrence	no recurrence	no re-challenge done
A, B	**N**	**A, B, O1, O, N**

4.1.4.

- Could the location/distribution of signs be caused by the treatment?

yes	no	not applicable
associative anatomical connection	no anatomical connection	
A, B	**N**	**A, B, O1, O, N**

Main question for section 4.1

- Is there a reasonable association in time and/or anatomical site?

yes	no	not known
reasonable association	no reasonable association	unknown
A, B	**N**	**O1 or O**

4.2. Pharmacological and/or immunological explanation

- known pharmacology, toxicology of the product (active substance and/or excipients)
- VMP concentrations in blood
- dose-effect relationship (degree of contribution of a product to the development of a reaction).

4.2.1.

Does the reported event fit into the toxicological profile or allergic potential of the product? Does the pharmacological/toxicological knowledge of the product fit the signs? Is the adverse event, the description of the clinical phenomena, consistent with or at least plausible, given the known pharmacology and toxicology of the product?

Do similar compounds cause events of this type?

- Does the reported event fit into the pharmacological/toxicological profile or allergic potential of the product?

yes	no	
A, B	**O1, O, N**	

4.2.2.

Has the product been overdosed? Did the product concentration in blood exceed the therapeutic concentration? Are concentrations in plasma known? What dose was used - overdose, correct dose, low dose, unknown dose? Did the adverse event show a dose-effect relationship?

- Did the adverse event show a dose-effect relationship (e.g. overdose)?

yes	no	not known
A, B	**A, B, O1, O, N**	**A, B, O1, O, N**

Main question for section 4.2

- Is there a reasonable association with the known pharmacological/toxicological profile, the allergic potential of the product and/or a dose-effect relation?

yes	no	
A, B	**O1, O, N**	

4.3. Presence of characteristic product or treatment related clinical or pathological phenomena

Are characteristic clinical or pathological phenomena present, which are related to the product or treatment?

Are there any measurable criteria to confirm the adverse event objectively, are confirming factors known (post mortem results, laboratory results)?

- Are additional data (laboratory tests, pathological findings) confirming clinical plausibility?

yes	no	not applicable/not available
A, B	**N**	**A, B, O1, O, N**

4.4. Previous knowledge of similar reports

a. from literature

b. from adverse events reported before

Are there any reports of this event known from literature? Is the event known and expected (described in SPC)? Have there been previous reports with these kinds of signs? Was this type of event reported before in an adverse event? Is the adverse event (generally) known to be potentially related to the product or treatment mentioned? *('adverse event' in this respect is the single pathological sign or the [majority of the signs in the] complex. 'Known' means published in literature or reported before and classified as A (probable) or B (possible)).*

- What about consistency of the reported event - is it already described in literature or SPC, has it been reported before?

yes	yes	no	no
described in literature or SPC, described in case record	observed before, but not fitting pharm./tox. profile	never observed before, but fitting pharm./tox. profile	never observed before, not fitting pharm./tox. profile
A, B	**B, O1, O, N**	**B, O1, O, N**	**O1, O, N**

4.5. Exclusion of other causes

Are there possible other causes for the adverse event? Is there another (also) likely cause? Is there another obviously more likely cause? Is this adverse event, to my best knowledge, unrelated to treatment? Use of combination of products/other products used?

Is the present disease contributing to signs? Is the health status of the animal contributing to signs? Are predisposing factors known? Are there other confirmed causes known (post mortem results, laboratory results, re-/de-challenge, other products used with pharmacological-toxicological potential to cause this event)?

- Is there any other explanation (confirmed, possible, no other explanation)?

yes	yes	no
confirmed	possible	none
N	**B, O1, O**	**A**

4.6. Completeness and reliability of the data in the case reports

- Is the reported information insufficient? Is there reason to doubt the reporting source/information?

yes	no	
O1, O	**A, B, N**	

5. Causality assessment by judging the answers to the questionnaire - minimum criteria

5.1. For inclusion in category A (probable)

Associative connection in time (**4.1 = yes**) and

Adverse event fits the pharmacological/toxicological profile of the product (**4.2 = yes**) and

No other equally plausible explanation (**4.5 = no**) and

No indication of insufficient/unreliable information (**4.6 = no**).

5.2. For inclusion in category B (possible)

Associative connection in time (**4.1 = yes**) and

Adverse event fits the pharmacological/toxicological profile of the product (**4.2 = yes**) and

Other equally plausible explanation possible (**4.5 = yes**) and

No indication of insufficient/unreliable information (**4.6 = no**).

or

There have been reports of the adverse event before (**4.4 = yes**) and

No indication of insufficient/unreliable information (**4.6 = no**) and

Associative connection in time (**4.1 = yes**) or adverse event fits the pharmacological/toxicological profile of the product (**4.2 = yes**).

5.3. For inclusion in category O1 (inconclusive)

Category O1 is for events where at least one of the answers from the questionnaire point to a causal relationship to the product or the treatment (A or B) but overall information is not sufficient to draw a conclusion. As some of these O1 classified events will recur and due to sufficient information in subsequent reports turn out to belong to B or even A category, they present an interesting issue for surveillance. For pharmacovigilance surveillance purposes O1 classified events can be seen as kind of interesting “precursors”.

Associative connection in time (**4.1 = yes**) and/or

Adverse event fits into the pharmacological/toxicological profile of the product (**4.2 = yes**) and/or

No other equally plausible explanation (**4.5 = no**) and

Inconclusive, unreliable or insufficient information (**4.6 = yes**).

5.4. For inclusion in category O (unclassifiable/unassessable)

Inconclusive, unreliable or insufficient information (**4.6 = yes**) which cannot be used to answer questions 4.1 to 4.5.

5.5. For inclusion in category N (unlikely)

Sufficient information exists to confirm that the product or treatment did not cause the adverse event (**4.5 = yes**) and

No indication of insufficient/unreliable information (**4.6 = no**).

6. Causality assessment for special kinds of reports and examples for application of the causality assessment guidance

Examples for the application of the causality assessment guidance as well as guidance on causality assessment for off-label use reports and reports of LEE for pharmaceuticals are attached as annexes.

7. Definitions

Lack of expected efficacy (LEE): The apparent inability of an authorised product to have the expected efficacy in an animal, according to the claims of the SPC and following use of the product in accordance with the SPC.

Off-label use: The use of a veterinary medicinal product that is not in accordance with the SPC including the misuse and serious abuse of the product.

VMP: veterinary medicinal product.

8. References

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uropean Commission (2004): Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

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Annex 1 Examples of adverse events for the application of the causality assessment guidance

Adverse event number	**A 1**	**A 2**	**B 1**	**B 2**	**B 3**	**B 4**
Therapeutic group	Antiemetic	Antibiotic	Antibiotic	Anaesthetic	Antibiotic	Sex hormones/modulators of the genital system
Active ingredients **Other products**	Dopamine D_2-antagonist	Sulfonamides	Tetracycline group Oxytocic agent	Injectable anaesthetic/narcotic agent α-adrenoceptor agonist, α_2-adrenoceptor antagonist	Fluoroquinolone Aminoglycoside antibiotic Fluorinated glucocorticoid	Antiprogestogenic agent
Species, Breed **Sex,** **Age, Weight**	Dog West Highland White Terrier 6 years	Dog	Horse	Dog, Cat	Dog, Labrador Retriever female 9 months 27 kg	Dog Shi Tzu 9 years
Nos. treated	1	1	1	2	1	1
Nos. reacted	1	1	1	2	1	1
Nos. died	0	0	1	0	0	0
Description of the event	For gastritis, a west highland white terrier was injected with the dopamine antagonist. Rapidly, it displayed an abnormal behaviour, aggression, abnormal gait, tremors and excitation. Within a few hours, it recovered spontaneously	Kerato-conjunctivitis sicca after three weeks of treatment	Minutes after i.v.injection staggering, collapse, death	5 minutes after injection respiratory depression, abnormal breathing	24 hrs after the treatment (for eczema in one ear) the dog showed diarrhoea. At this time the dog began oestrus. The treatment was suspended and the diarrhoea disappeared in two days.	For a suspicion of pregnancy, a female Shih Tzu was injected subcutaneously with 2 ml of an antiprogestogenic agent. During the injection, the dog moved and the veterinarian suspected intravenous injection (haematoma on the injection point). A few minutes later, the dog staggered, displayed recumbency, bradycardia, dyspnoea and shock. With a symptomatic treatment (diuretic, 2 different glucocorticoids), the signs decreased within one hour. The dog displayed then anorexia, weight loss, diarrhoea and depression during 4 days.
ABON	**A**	**A**	**B**	**B**	**B**	**B**

Adverse event number	**A 1**	**A 2**	**B 1**	**B 2**	**B 3**	**B 4**
Reasons for coding the example	A: Chronology and troubles are very compatible with a suspected adverse effect of the dopamine antagonist. Numerous similar reports are already registered, no equally plausible explanation.	A: characteristic reaction, known suspected adverse effect, time of onset and dose fit in, no equally plausible explanation.	B: Onset of signs almost immediately following i/v administration, observed event consistent with previous reports; a second product (oxytocic agent, i.v.) had been administered to the animal at approx. the same time. Horse not a target species. Product past expiry - other equally plausible explanation.	B: There is a likely causal relationship between event and product, but it is difficult to distinguish the product responsible for the adverse event– co-medication always means there is another plausible explanation.	B: It is possible that the antibiotic affected the gut flora and caused the diarrhoea. Some cases are described in literature, but another possible explanation cannot be excluded.	B: The time to onset is very suggestive of an effect of the administration of the antiprogestogenic agent. The observed troubles cannot be considered as suggestive but some similar cases are already registered.

Adverse event number	**O 1**	**O 2**	**N 1**	**N 2**
Therapeutic group	Vaccine	NSAID	Antiparasitic (spot on)	Agents acting on the autonomic nervous system
Active ingredients **Other products**	Vaccine	Arylpropionic acid derivative	Avermectin	Indirect acting sympathomimetic
Species, **Breed** **Sex,** **Age,** **Weight**	Cat	Dog 3 years	Dog Basset 8.5 years	Dog
Nos. treated	1	1	1	1
Nos. reacted	1	1	1	1
Nos. died	0	0	0	1
Description of the event	A healthy cat becomes ataxic the day after a vaccination. No fever or other signs, and no signs of other diseases. The signs disappear after a few days.	One week after treatment slight alopecia, swelling of eye lids	Call before examination. The dog was treated with one pipette of the avermectin-containing product (20-40 kg). A few hours later, the dog displayed hind limb paresis. Note: the owner carried the animal to get out of the car. In fact, after examination, the animal displayed a protrusion of a vertebral disk.	Hours later halitosis, vomiting, diarrhoea, death.
ABON	**O1**	**O**	**N**	**N**
Reasons for coding the example	O1: Time of occurrence could point to post-vaccination reaction, but too uncertain for an overall B classification. Not classifiable with the knowledge at the moment.	O : Report seems to be totally unreliable. O is based on the insufficient information that was available to draw any conclusion.	N: The diagnosis of a protrusion of a vertebral disk permits to exclude the role of the avermectin.	N: Animal was ill prior to treatment; end stage renal disease diagnosed at post mortem

Annex 2 Assessment of adverse events recorded as “off-label use” reports

Background

The scope of veterinary pharmacovigilance as defined in Article 73 of Directive 2001/82/EC does not only cover adverse events in animals to VMPs used under authorised conditions of use, but also any available information related to reports after off-label use of VMPs.

Reports of adverse events may be obtained on VMPs used outside the terms of the marketing authorisation e.g. use in non-authorised species, use in non-authorised species for indications which are not authorised, use at doses or via application routes differing from those set out in the relevant SPC. Such reports can provide useful information on the safety of the VMP and should be recorded and reported to the competent authorities under the responsibility of the qualified person responsible for pharmacovigilance. Periodic safety update reports should include all (serious and non-serious) reports of off-label use of the VMP.

Definition

Off-label use: the use of a VMP that is not in accordance with the SPC, including the misuse and serious abuse of the product [as defined in Article1 (16) of Directive 2001/82/EC].

Other terms often used in this context should not be used to avoid misunderstanding, e.g.:

- extra-label use
- extra-label drug use (ELDU)

Criteria to be considered when classifying adverse events as “off-label use”

In general, the use of a VMP has to be in accordance with the SPC. However, situations occur where medicinal products are used – on purpose or unintended - in a way which is not covered by the SPC. Experience from Member States shows that the frequency of under-reporting for off-label use is much higher and follow-up is more difficult to perform than for ‘regular’ events occurring after recommended use. Often veterinary surgeons are hesitant to report an adverse event due to the off-label-use or to give further details, which would be necessary for the comprehensive assessment of the event. One reason for this could be the fear of legal and/or financial consequences.

Off-label use reports can provide useful information on the safety of the given VMP, e.g. it can reveal risks of incorrect administration and should be recorded under the responsibility of the person responsible for pharmacovigilance and reported to the competent authorities in the same way as for all other adverse events. The existing reporting procedures should be used.

Reports of adverse events concerning off off-label use may be obtained:

- on products used outside the terms of the marketing authorisation e.g. use of a product in non-authorised species, use at doses differing from those set out in the SPC and product information.

  There are various possibilities where the use of a VMP is not in accordance with the SPC:

  - Target species not authorised (special case: ‘cascade’, see below)
  - Category or age of animal not authorised

Some products are only authorised for specific animal sub-categories e.g. a vaccine may be only recommended for active immunisation of sows and gilts or treatment is only authorised for a specific age-category.

- o Use during pregnancy, lactation or lay

Very often the treatment or vaccination of pregnant and lactating animals is not recommended as this has not been investigated.

- o Breed not authorised
- o Incorrect route of administration
- o Incorrect injection site

For several products the injection site is recommended e.g. birds should be given vaccines subcutaneously into the lower part of the neck.

- o Wrong dosage or treatment scheme
- o Wrong reconstitution of the medicine

This may happen with products such as live vaccines which are reconstituted with a different diluent or another vaccine.

- o Use of a VMP with an expired date.

- when products are used concurrently

All medication used or administered over at least a one one-week period preceding the adverse event should be provided when available. However, a large number of VMPs, mostly vaccines, state in the SPC that no information is available on safety and efficacy when used with other products (vaccines). A decision to use the product before or after any other product therefore “needs to be made on a case to case basis”. This reflects the need for collecting more information on concurrent use. It is therefore recommended to equally provide details of all medication used over at least a one week period preceding the adverse event.

At the same time it should be clear that if another product has been used concurrently, any adverse event report for a product used in line with the SPC (and according to the SPC recommendation on concurrent use had to be made on a case to case basis) will not be classified as off-label.

- on products used outside the terms of the marketing authorisation but in conformity with the provisions of Article 10 or 11 of Directive 2001/82/EC - use of unauthorised VMPs

In Articles 10 and 11 of Directive 2001/82/EC an exception is mentioned known as the prescribing "cascade". The "cascade" allows the veterinary surgeon to use products following a series of decisions providing that no authorised product is available for the treatment of that specific patient. The veterinary surgeon may prescribe:

i. A product authorised in their Member State for that condition in another species or a product authorised for another condition but in the same species

ii. If no such product exists, an appropriate authorised human medicine or a VMP authorised in another EU Member State

iii. If no such product exists, a product prepared extemporaneously by an authorised person in accordance with a prescription.

- use of illegal medicines (misuse, abuse).

Causality assessment for adverse events after off-label use

To ensure consistency in using the ABON-system by pharmacovigilance personnel in competent authorities as well as in industry, common approaches to analyse, assess and code reported off-label use events should be established.

The overall assessment of off-label reports is essentially the same as for 'regular' reports (following recommended use of the VMP) and follows the rules laid down in Volume 9B resulting in a causality assessment according to the ABON scheme: A (probable), B (possible), O1 (inconclusive) or O (unclassifiable/unassessable) or N (unlikely). The guidance for causality assessment in Volume 9B does not mention the use of a product according or against the instructions for use as being relevant for the causality assessment.

However, the experience so far has revealed a tendency to classify such events as N or O causality. The fact that the product per definition is not used as recommended may suggest that these events are classified differently.

However, it has to be remembered that causality assessment takes into consideration both product and treatment: it addresses the issue of whether and how the reported treatment with the product and the reported adverse events are causally related - irrespective whether the product is used according to the recommendations for use or off-label - whereas regulatory actions will generally be triggered by at least potentially product related causality. Nevertheless, any at least possibly causally related serious off-label events where a potential risk using the product incorrectly has been identified may necessitate changes in SPC (e.g. warnings or explanation of correct use).

Annex 3 Assessment of adverse events recorded as lack of expected efficacy (LEE) concerning pharmaceuticals

Background

Directive 2001/82/EC cites the failure to demonstrate efficacy as a reason for refusal or revocation of a marketing authorisation. It is an important aspect of the consideration of the benefit-risk balance of a product. It is felt necessary to provide a basis for a common understanding and uniformity in assessing adverse events recorded as LEE.

For the time being guidance on LEE is provided for pharmaceutical only, vaccines are excluded. Guidance on LEE concerning vaccines will be provided in due time.

Criteria to be considered when classifying adverse events as LEE

According to the definition of Volume 9B, "LEE may be defined as the apparent inability of an authorised product to have the recognised expected efficacy in an animal, according to the claims of the SPC and following use of the product in accordance with the SPC."

It was concluded that LEE should only be considered as such when the VMP was administered according to the claims of the SPC and following use of the product in accordance with the SPC.

Pharmaceutical overdose events are usually exceptions to the requirement that qualifying an event as LEE the VMP needs to be administered according to the claims of the SPC and following use of the product in accordance with the SPC. The information related to the therapeutic indications, the route of administration, the dosage and the target species (age and all other animal characteristics data) should be checked and analysed from a critical point of view before assessing such an event which is identified as LEE by the reporters. The laboratory investigations/post-mortem examination to confirm the involvement of the product or to establish a differential diagnosis are very important to thoroughly assess these events.

Events should be recorded as LEE after having been administered at a dose higher than that recommended. For instance, if a VMP administered at twice the recommended dose is not efficacious, it is reasonable to assume that it should be non efficacious when administered at the recommended dose. In certain circumstances, products used at higher doses than those recommended can give rise to cases of LEE, e.g. anthelmintic resistance on a farm.

Factors to take into account for the causality assessment of LEE reports

To ensure consistency in using the ABON-system by pharmacovigilance personnel in competent authorities as well as in industry, common approaches to analysing, assessing and coding of reported adverse events have been adopted.

Eight main factors should be taken into account: the conditions of administration, clinical or pathological signs, clinical explanation, environmental situation, onset of clinical signs, other causes, hygiene conditions, quality defect, reliability of data, in particularly the reliability of diagnosis i.e. diagnosis made by a veterinary surgeon or animal owner versus clinical diagnosis confirmed by laboratory and post mortem investigations) and published data. For LEE reports it is essential to substantiate clinical observations by laboratory data (post-mortem reports, microbiological and/or parasitological investigations). A determined effort should be made to gain additional laboratory data supporting clinical observations when the LEE report is received without this information.

Causality assessment of LEE reports

The following approach compiles guiding questions for each aspect, which are meant as examples and not intended to be exhaustive. They facilitate finding the answer to the main questions, which are listed at the end of each section (c.f. Table). According to the question and the information available, a choice of 2 or 3 answers is given: yes, no or unknown, some answers point towards N coding. The overall interpretation of the answers point towards A (probable), B (possible), O1 or O (inconclusive or unclassifiable/unassessable) or N (unlikely). In the future, an algorithm could be a useful tool to achieve consistency in causality assessment.

1. Was the VMP used in accordance with recommendation of the marketing authorisation?		
	1.1. Were the therapeutic indications respected? [A clear NO points towards N (unlikely)]	
	1.2. Were the characteristics of the animals to which the VMP has been administered in compliance with the SPC recommendations (species, age etc.)? [A clear NO points towards N (unlikely)]	
	1.3. Was the dose administered correct (in compliance with the SPC recommendations)? [A clear NO points towards N (unlikely)]	
	1.4. Were the treatment length, the therapeutic regimen correct or in compliance with the SPC recommendation? [A clear NO points towards N (unlikely)]	
	1.5. Was the administration route used in compliance with the SPC recommendation? [A clear NO points towards N (unlikely)]	
	1.6. Was there a clear medicinal contra-indication for the products administered concurrently? [A clear YES points towards N (unlikely)]	
	Depending on the answers to questions 1.1. to 1.6, an overall assessment of the information available leads to conclude that the recommendations of the SPC :	
	o have been followed (all YES)	Points towards B (possible) or A (probable)
	o have not been followed (one NO is enough)	Points directly towards N (unlikely)
	o quite difficult to conclude (unknown)	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable)
2. Does the onset of the *clinical signs* occur after the treatment period necessary to establish efficacy and during the period of the efficacy of the product? [onset and evolution of the clinical signs and/or presence of the pathogens in absence of specific clinical signs (presence of parasites etc.)]?		
	Was the LEE identified during the efficacy period of the product? (if one efficacy period of the product is known)? [a clear NO points towards N (unlikely)]	
	YES	Points towards B (possible) or A (probable)
	NO	Points directly towards N (unlikely)
	It is not possible to conclude	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable)
3. Did the clinical signs fit the condition for which the product is indicated?		
	3.1. Is there a reasonable consistency between clinical signs of the adverse event recorded and those of the indications mentioned in the SPC? Are the clinical signs recorded specific or in line with of the pathology treated?	
	YES	Points towards B (possible) or A (probable)
	NO	Points directly towards N (unlikely)
	It is not possible to conclude	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable)

4. Are there any measurable criteria to explain the event objectively? Has the diagnosis been confirmed? (post mortem results, laboratory results to confirm the diagnosis made before or after treatment of the animals or observations)?		
	YES NO/Unknown/Not applicable	Points towards A (probable) Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable) or N (unlikely)
5. Is there any information available concerning the farm environment that could explain the pathology (illness) despite animals having received treatment (if applicable)?		
	5.1. Was (were) the animal health status good? 5.2. Was the infestation pressure high? 5.3. Is there any information related to concomitant pathology and the medical history of the breeding/ farming and/or of the animal? Are there reports of resistance to the product on the farm or in the area where the event occurred? 5.4. Were zoo-technical and environmental measures taken? Were the hygiene conditions satisfactory? Were the farm management practices acceptable?	
	An overview of the information allows conclusion that the environment factors	
	Could explain in part (YES)	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable)
	Did not play any role (NO)	Points towards A (probable)
	It is not possible to conclude	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable)
6. Is there any indication to confirm that the event is due to another cause that could explain the clinical signs recorded?		
	There is a confirmed cause or aetiology indicating that the event is not due to/linked to the non-efficacy of the product	Points directly towards N (unlikely)
	There are other plausible causes/explanations	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable)
	There are no other causes/ explanations	Points towards A (probable)

7. Is a quality problem suspected?		
	A quality defect is suspected (e.g. storage conditions not respected)	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable)
	A quality defect is excluded (batch analysis available)	Points towards A (probable)
	No information available	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable) or A (probable)
	A quality defect has been clearly identified (batch analysis, expired batch)	This event should be assessed A (probable) This type of adverse event should be entered in EVVet but it should be clearly identified that the event is due to a batch quality defect. Indicate if the batch has been recalled.
8. Previous knowledge of similar reports concerning the LEE?		
	8.1. There are scientific data	
	8.2. There are similar events reported	
	YES	Points towards B (possible) or A (probable)
	NO	Points towards B (possible) or O1 (inconclusive) or O (unclassifiable/unassessable) or A (probable)
Is the reported information insufficient? Is there reason to doubt the reporting source/information?		
	Yes	Points towards O1 (inconclusive) or O (unclassifiable/unassessable)