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Committee for Veterinary Medicinal Products

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Guidance notes on the use of VeDDRA terminology for reporting suspected adverse events in animals and humans

Introduction - Updated

The purpose of these notes is to explain the principles of Veterinary Dictionary for Drug Related Affairs (VeDDRA) terminology and to provide advice about its use. The aim is to achieve a harmonised approach to the selection of VeDDRA terms.

VeDDRA has a four-level hierarchical structure as follows:

SOC – system organ class
HLT – high level term
PT – preferred term
LLT – low level term

The relationship between the SOC and the LLT is mono-axial i.e. a specific LLT is only available in one specific SOC. In cases where similar LLTs exist in other SOCs, an LLT contains a cross reference to the location of the other terms. In order to achieve medically relevant groupings for analysis of adverse events, the relation between PTs and LLTs covers two different concepts, allowing an LLT to be either a synonym or a sub-classification of a particular PT. For example, the PT 'Anaphylaxis' includes the LLTs 'Anaphylaxis' and 'Anaphylactoid reaction'. In VeDDRA, the terminologies in the SOC and the HLT are plural, with the PT and the LLT being in the singular (unless a particular term would not otherwise make medical sense). In addition, any PT term is available as an LLT too.

The selection of VeDDRA terms to describe an adverse event should be at LLT level. The LLT selected should be appropriate for the clinical signs described by the reporter, but also taking into consideration that this reflects the correct PT and SOC grouping. LLTs involving NOS (not otherwise specified) should only be chosen when a more specific LLT is not available for coding. Analysis will normally be carried out at PT level. There are several situations where there could be more than one choice at LLT level, sometimes with different results at SOC level. Some of the more frequent situations are discussed below. It is not the intention to restrict the choices, but to encourage a standard approach so that the results of analysis will be consistent and valid. If it is clear that a reported clinical sign occurred before administration of the product, or if it is known that it was due to the disease being treated or another specific cause (e.g. the reporter mentions dietary ketoacidosis) it should not be coded using VeDDRA

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as this would not be classified as an adverse event related to a veterinary medicinal product. However, if there is any element of doubt or the sign(s) worsened after the administration of the product, then the clinical sign(s) should be coded in the usual way and this situation should subsequently be considered when analysing adverse event data. Note: this requirement does not apply to 'Lack of efficacy' reports (see Section 25.3 Lack of efficacy for more detailed guidance).

In general, it is preferable to avoid coding the same or similar clinical signs multiple times (e.g. emesis and vomiting) unless the LLTs relate to different PTs as this may impact on subsequent analysis. However, there are some PTs e.g. gingival disorder, where multiple LLTs may need to be coded (e.g. gum bruising, gingival hyperplasia, gum pain and gingivitis) resulting in the PT being coded multiple times. Information on signs observed after re-challenge is useful for determining the causal association with the veterinary medicinal product administered.

It should also be noted that the VeDDRA terms list is deliberately kept as a non-exhaustive list where the focus is to cover the most commonly used terms and situations and to learn from practice through the feedback from users as part of the yearly revision exercise. In addition, the list is not intended to provide terms that would define a specific disease or syndrome.

Version history: in this version (EMA/CVMP/PhVWP/288284/2007-Rev.18[1]) a table of contents was introduced to facilitate access to the guidance available and relevant changes were made to the following sections: Introduction; 13.1. Medication errors and intentional misuse; 26.1. Not otherwise specified (NOS)(new section); and 26.6. Embolism and thromboembolism.

[1] for use with VeDDRA EMA/CVMP/PhVWP/10418/2009-Rev.17 (EVVet implementation v22)

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1. Application site disorders

No additional guidance.

2. Behavioural disorders

2.1. Distress

Distress is a term often used by reporters to describe an animal which is not behaving normally, yet the reaction is rarely associated with a behavioural disorder. In VeDDRA the term is located in this SOC, so in cases in which it is the only reported sign and the overall picture is not clear, it may be necessary to seek advice from the qualified person for pharmacovigilance (QPPV) or the national competent authority (NCA) to achieve consistency in the recording of this term.

SOC	HLT	PT	LLT
Behavioural disorders	Other behavioural disorders	Anxiety	Distress

Stress is a state of mental or emotional strain or tension resulting from adverse or demanding circumstances and is often reported by animal owners. Animals show stress by behaving differently than usual and this should be coded by 'Behavioural disorder NOS'.

3. Blood and lymphatic system disorders

No additional guidance.

4. Cardio-vascular system disorders

No additional guidance.

5. Digestive tract disorders

5.1. Induced vomiting

Vomiting may be induced in order to treat a condition. In such cases it would not be appropriate to record vomiting as a clinical sign involved in the adverse reaction if an emetic had been administered.

5.2. Oral obstruction

The LLT term 'Oral obstruction' which maps to the PT 'Oral cavity disorders NOS' should be used for reports where the chew gets stuck between the teeth or in the mouth of the animal. It should only be reported together with other signs such as e.g. hypersalivation or dysphagia.

6. Ear and labyrinth disorders

No additional guidance.

7. Endocrine system disorders

No additional guidance.

8. Eye disorders

No additional guidance.

9. Hepato-biliary disorders

No additional guidance.

10. Immune system disorders

10.1. Anaphylaxis and hypersensitivity reactions

The clinical signs of anaphylaxis or hypersensitivity reactions can vary according to the species and, in less severe cases, some of the signs are not obviously part of the syndrome, so it is sometimes a matter of opinion as to whether the reaction was anaphylaxis or hypersensitivity reaction. **If the reporter has described it as such**, it should be coded as anaphylaxis or hypersensitivity reaction using the appropriate LLT.

There are four and six terms, respectively, at LLT level, all of which are described as 'Anaphylaxis' and 'Hypersensitivity reaction' at PT level. Therefore, from the point of view of analysis, the choice of LLT term will make no difference

SOC	HLT	PT	LLT
Immune system disorders	Allergic conditions	Anaphylaxis	Anaphylaxis
Immune system disorders	Allergic conditions	Anaphylaxis	Anaphylactic shock
Immune system disorders	Allergic conditions	Anaphylaxis	Anaphylactoid reaction
Immune system disorders	Allergic conditions	Anaphylaxis	Anaphylactic-type reaction
Immune system disorders	Allergic conditions	Hypersensitivity reaction	Allergic pruritus
Immune system disorders	Allergic conditions	Hypersensitivity reaction	Allergic skin reaction
Immune system disorders	Allergic conditions	Hypersensitivity reaction	Allergy NOS
Immune system disorders	Allergic conditions	Hypersensitivity reaction	Allergic reaction
Immune system disorders	Allergic conditions	Hypersensitivity reaction	Hypersensitivity NOS
Immune system disorders	Allergic conditions	Hypersensitivity reaction	Hypersensitivity reaction

[1] NOS = Not otherwise specified

If the reporter does not mention a clinical sign mapping to a LLT linked **to the PTs 'Anaphylaxis' or 'Hypersensitivity reaction'** but the case narrative matches with one of the following two definitions, then the reaction should be recorded as anaphylaxis or hypersensitivity

reaction accordingly. Only code signs that occur after the product was administered. In all cases, use medical judgement for the final decision.

1. **ANAPHYLAXIS** is a severe allergic reaction that appears rapidly and is **life-threatening**. It is the most severe form of the Type 1 hypersensitivity mechanism. The clinical signs are very varied **but general systemic signs are always present**. The clinical picture is most often dominated by the presence of shock (acute systemic circulatory failure, altering the oxygenation and metabolism of various tissues and organs, which can lead to irreversible damage) with changes in mucous membrane colour (pale or bluish), changes in capillary refill time, tachycardia, a drop in systemic arterial pressure and a drop or loss of consciousness. Untreated anaphylactic reactions lead irrevocably to cardiovascular collapse.

Anaphylaxis should be coded when the following criteria are fulfilled:

Acute onset (up to 2 hours) of an illness with rapid progression of clinical signs AND including at least two of the following:

1) involvement of the skin and/or mucosal tissue (e.g. pruritus, oedema, facial swelling)
2) respiratory compromise (e.g. dyspnoea, bronchospasm, stridor, hypoxaemia)
3) clinical signs of cardiovascular compromise or end-organ dysfunction (e.g. hypotension, syncope, incontinence).

All the reported clinical signs should also be listed at LLT level.

2. **HYPERSENSITIVITY REACTION** is more moderate in intensity than anaphylaxis and **is not life-threatening.** Clinical signs are similar to those observed in anaphylaxis but are **clinically less intense and do not lead to cardiovascular collapse.**

Hypersensitivity should be coded when the following criteria are fulfilled:

Acute or non-acute (up to 72 hours) onset of clinical signs without respiratory compromise or clinical signs of cardiovascular or end-organ dysfunction and where three or more signs listed in Table 1, for the respective species, are reported. However, if the reaction is not considered to be a hypersensitivity reaction, hypersensitivity should not be coded and the justification should be described in the narrative.

Note: When one or two clinical signs are reported (e.g. vomiting and defecation, or sweating and coughing etc.) they should generally not be coded as hypersensitivity, except if other information in the case indicates hypersensitivity.

All the reported clinical signs should also be listed at LLT level.

Table 1. The main clinical signs of anaphylaxis or hypersensitivity reactions in individual species are listed below (NB this is not and exhaustive list)

Species	Clinical signs
Dog	Excitement, urticaria, pruritus, angioedema including facial oedema, eyelid oedema, lip oedema, Quincke's oedema, vomiting, defecation, dyspnoea, collapse, convulsions.
Cat	Pruritus, angioedema including facial oedema, eyelid oedema, lip oedema, Quincke's oedema, salivation, vomiting, dyspnoea, incoordination, collapse.
Horse	Shivering, sweating, incoordination, coughing, dyspnoea, diarrhoea, colic, collapse, urticaria and pruritis.
Cow and sheep	Urticaria, restlessness, pruritus, angioedema including eyelid oedema, mammary gland oedema or congestion and vulvar oedema or congestion, defecation, urination, coughing, dyspnoea, cyanosis, bloat, collapse.
Pig	Dyspnoea, cyanosis, pruritus, collapse, vomiting, diarrhoea.

Anaphylaxis and hypersensitivity reactions should be clearly differentiated from other systemic post-vaccine reactions and vagal shock.

'Vagal shock' is an LLT term which maps to 'Circulatory shock' at the PT level. The clinical picture is composed of bradycardia, hypotension, cerebral hypoperfusion. Loss of consciousness may result from these alterations. The prognosis is not life-threatening, except for traumatic injury following a fall during syncope. Vagal malaise is not directly related to the veterinary medicinal product (VMP) but to the treatment environment (stress, pain, fear).

It is advised that 'Vagal shock' should only be coded if specifically mentioned by the original reporter. Marketing authorisation holders (MAHs) and national competent authorities (NCAs) should not code this term based on an interpretation of case narratives describing collapse-type events within seconds following product administration. 'Circulatory shock' or 'Circulatory collapse' is more appropriate terms to code these types of events. It is also important to differentiate between these events and those of suspected anaphylaxis or hypersensitivity reaction as described above.

'Neurological shock' (for example that associated with procaine penicillin administration) should be coded using the LLT 'Shock' which maps to the PT 'Circulatory shock'.

11. Investigations

11.1. Investigations and diagnostic test results

The principles of VeDDRA terminology were established to describe clinical signs or other easily detectable clinical information. However, as the availability of diagnostic equipment and services to veterinary practices continues to develop, further terms were requested and a SOC was created to group all these investigation results in one place and a selection is provided in the table below. If the appropriate term is not available in VeDDRA, one of the following terms should be selected and details of the test should be provided in the narrative.

SOC	HLT	PT	LLT
Investigation	Abnormal cytology	Abnormal cytology	Abnormal cytology
[…]	[…]	[…]	[…]
Investigations	Abnormal imaging	Abnormal image	Abnormal image NOS
[…]	[…]	[…]	[…]
Investigations	Abnormal physical examination	Abnormal rectal palpation	Abnormal rectal palpation
[…]	[…]	[…]	[…]
Investigations	Other abnormal test result NOS	Other abnormal test result NOS	Other abnormal test result NOS
[…]	[…]	[…]	[…]
Investigations	Histological investigations	Abnormal histology NOS	Abnormal histology NOS

It should be noted that the PT 'High adrenocorticotropic (ACTH) hormone' should be used only to code cases where the levels of this hormone have been measured, for example in the investigation of pituitary pars intermedia dysfunction. This term maps to 'Pituitary investigations' at HLT. Signs relating to adrenal gland investigations (such as Abnormal adrenocorticotropic hormone (ACTH) stimulation test) should be coded as such under the HLT 'Adrenal investigations'.

11.2. Necropsy

Reports which include results from necropsy (or autopsy) should follow the principle that all abnormal necropsy findings which have a plausible temporal association to product administration should be coded using the appropriate LLT unless findings are known to be associated with the disease being treated.

Pathologic findings which indicate prior or ongoing health issues or other incidental findings should be mentioned in the case narrative only if they are particularly relevant (e.g. due to pre-existing pathology the animal was particularly prone to the adverse event).

When a necropsy (or autopsy) report, or its findings, are reported for a case the LLT 'Necropsy performed' should be coded to indicate the case includes necropsy findings.

The list of VeDDRA terms in a report should never be limited to the LLTs 'Death' and 'Necropsy performed' only.

12. Mammary gland disorders

No additional guidance.

13. Medication errors and intentional misuse – Updated

13.1. Medication errors and intentional misuse including product use errors

The terms in this SOC shall aid the identification and coding of 'special situations', some of which are described in the Guideline on veterinary good pharmacovigilance practice (VGVP) module: Collection and recording of suspected adverse events for veterinary medicinal products (EMA/306663/2021).

A medication error is any unintentional and/or preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of veterinary healthcare professionals or other individuals handling the medication such as pet owners and animal handlers. Deliberate or intentional use of a medicinal product is not considered a medication error. Such events may occur at any point during the medication use process, which includes prescribing, dispensing, administering the medication and monitoring the patient. The naming, labelling, packaging configuration, and other design elements (e.g. container closure, graphics, etc.) of the medicinal product may contribute to a medication error.

SOC	HLT	PT	LLT
Medication errors and intentional misuse	Accidental exposure to product	Accidental exposure	Accidental exposure
Medication errors and intentional misuse	Device use issues	Device use issues	Device use issues NOS
Medication errors and intentional misuse	Intentional misuse	Intentional misuse	Intentional misuse
Medication errors and intentional misuse	Medication and product use errors NOS	Administration error	Administration error
Medication errors and intentional misuse	Medication and product use errors NOS	Dispensing error	Dispensing error
Medication errors and intentional misuse	Medication and product use errors NOS	Medication error NOS	Medication error NOS
Medication errors and intentional misuse	Medication and product use errors NOS	Monitoring error	Monitoring error
Medication errors and intentional misuse	Medication and product use errors NOS	Prescribing error	Prescribing error

LLT Accidental exposure: Accidental exposure should be used to code events with unintended exposure to a veterinary medicinal product e.g. exposure via a treated animal (by licking, eating faeces) or in cases of medication error, such as human exposure via accidental ingestion of a veterinary medicinal

product. This can be applied to environmental incidents when the exposure is accidental; if exposure was deliberate then it would be intentional misuse. Note: an adverse event following consumption of carcasses containing a veterinary medicinal product would be considered LLT 'environmental incident' and not 'accidental exposure'.

LLT Device use issues NOS: where problems related to the handling of a product device (by the user) or with the acceptance of the device (by the animal) are reported, the PT/LLT 'Device use issues NOS' is recommended and details should be provided in the narrative. If the device causes an injury, then LLT 'Accidental device injury' should be used. If the problem with device use is due to a product defect, then the VeDDRA HLT/PT/LLT 'Product defect NOS' should be used instead.

LLT Intentional misuse: Intentional misuse is defined as deliberate use of a veterinary medicinal product or a medicinal product for humans used in animals for a purpose not consistent with applicable local legal or medical guidance, whether or not clinical signs are observed. Intentional misuse is also intentional use of a veterinary medicinal product in humans, unless permitted by legal provision, whether or not clinical signs are observed. Misuse may be instigated by a veterinarian, other animal healthcare professional, animal owner or other individual.

Examples:

- Humans who take veterinary medicinal products for doping, as appetite suppressants, for recreational use, to treat themselves (against lice, for example), to attempt suicide (even if already coded with two specific LLTs 'Suicide attempt' and 'Suicide completed') etc.
- Animal reports where the veterinarian or owner deliberately deviates from the marketing authorisation recommendations and/or applicable local regulations / guidance.
  Note: off-label use, as allowed by local regulation / guidance is not intentional misuse.

LLT Prescribing error: to be used when a veterinarian or equivalent prescribes the wrong medicine or gives wrong instructions / dosage information by mistake (this does not include administration of the wrong medicine by mistake by a veterinarian = 'administration error')

LLT Dispensing error: to be used when the animal owner is dispensed incorrect medication / given wrong dosing information / other instructions by mistake in the process of the medicine being dispensed to the animal owner. (If the incorrect information is provided by a veterinarian, then this should be considered a 'prescribing error').

LLT Administration error: includes a veterinarian making an error while directly administering a product to an animal, a veterinary technician erroneously choosing the wrong veterinary medicinal product for an inpatient, giving the wrong dose, via the wrong route, or the owner erroneously gave the wrong dose etc.

LLT Monitoring error: to be used where the adverse event involves medication for which specific monitoring is specified on the product information (PI) and this has not been performed properly (e.g. diabetes mellitus).

LLT Medication error NOS: to be used in adverse event reports where a medication error occurred but no specific information is available or if a specific error is reported but no suitable LLT is available, then LLT 'Medication error NOS' is recommended and details should be provided in the narrative. Also to be used when an error was intercepted before the medicine reached the patient.

14. Metabolism and nutrition disorders

No additional guidance.

15. Musculoskeletal disorders

No additional guidance.

16. Neoplasia

16.1. Metastatic neoplasia and secondary malignancy

Secondary malignancies are cancers caused by treatment with radiation or chemotherapy. They are unrelated to the first cancer that was treated and may occur months or even years after initial treatment. They should not, therefore, be confused with metastatic tumours which are related to the primary tumour and are the result of local, haematogenous or lymphatic spread of malignant cells from the primary tumour. Consequently, these terms are coded differently.

SOC	HLT	PT	LLT
Neoplasia	Neoplasia NOS	Metastatic neoplasia	Metastatic neoplasia
Neoplasia	Neoplasia NOS	Metastatic neoplasia	Metastatic tumour
Neoplasia	Neoplasia NOS	Neoplasia NOS	Secondary malignancy

16.2. Sarcoma

The LLT term 'Injection site sarcoma' should be used to describe sarcomas at injection sites. Other LLT terms used to describe sarcomas should be avoided because of the differences at PT level which would exclude them from analysis. For example:

SOC	HLT	PT	LLT
Neoplasia	Injection site neoplasms	Injection site sarcoma	Injection site sarcoma
Neoplasia	Application site neoplasms	Application site sarcoma	Application site sarcoma
Neoplasia	Skin and appendages neoplasms	Skin and/or appendage neoplasm NOS	Skin sarcoma NOS
Neoplasia	Connective tissue neoplasms	Fibrosarcoma	Skin fibrosarcoma

17. Neurological disorders

No additional guidance.

18. Other event

18.1. Parent – offspring events

The LLTs in PT 'Parent-offspring event' shall aid the identification and coding of special scenarios as described in the Guideline on veterinary good pharmacovigilance practices (VGVP) module: Collection and recording of suspected adverse events for veterinary medicinal products (EMA/306663/2021), 'Suspected adverse event reports for offspring exposed through a parent'.

These terms must be used in addition to other relevant VeDDRA terms (e.g. clinical signs, product defect) of the reacting animals. The list of VeDDRA terms in a report should never be limited to one of these terms.

SOC	HLT	PT	LLT
Other event	Other event	Parent-offspring event	Parent-offspring event
Other event	Other event	Parent-offspring event	Father and offspring event
Other event	Other event	Parent-offspring event	Mother and offspring event
Other event	Other event	Parent-offspring event	Offspring-only event

- LLT 'Parent-offspring event' should be used in adverse events where an unidentified parent was treated and it is suspected that the treated parent and offspring are affected by this treatment.
- LLT 'Mother and offspring event' should be used in adverse events where the mother was treated and it is suspected that mother and offspring are affected by this treatment.
- LLT 'Father and offspring event' should be used in adverse events where the father was treated and it is suspected that father and offspring are affected by this treatment.
- LLT 'Offspring-only event' should be used in adverse events where one or both parents were treated and it is suspected that only the offspring is/are affected by this treatment.

Important scenarios to consider:

- In case of adverse events observed with abortion, none of the parent-offspring event VeDDRA terms should be used.
- In cases of LEE reported for veterinary medicinal products (VMPs) applied to parent animal(s) and which are indicated to reduce foetal mortality, abortion or transmission of a pathogen to the offspring, the "lack of efficacy" applies to the parent and does not refer to the offspring, as the VMP should have been effective in the parent animal(s). In this case none of the parent-offspring event VeDDRA terms should be used.
- In cases of adverse events observed with stillbirth, the relevant parent-offspring event VeDDRA term should be used, in addition to all other relevant VeDDRA terms and, at the very least, the VeDDRA term "Stillbirth".

In cases of LEE reported for VMPs applied to parent animal(s) and ***which are indicated to protect the offspring*** *(for example: vaccines that are administered to the parent to protect the offspring by transferring specific antibodies via the colostrum)* and insufficient efficacy can be assumed in the

offspring, the 'Offspring only event' VeDDRA term should be used in addition to the relevant lack of efficacy VeDDRA term. The treated animal(s) still refers to the parent animal(s).

18.2. Literature report

Adverse event reports which are identified in literature should be coded with the LLT 'Literature report' to aid the identification of literature cases especially in signal management.

SOC	HLT	PT	LLT
Other event	Other event	Literature report	Literature report

18.3. Uncoded sign

The LLT 'Uncoded sign' should ONLY be used when there is no existing VeDDRA term to code the clinical sign(s) observed. Further detail relating to the clinical sign should be explained in the narrative of the adverse event report. Where appropriate, a proposal for a new VeDDRA term should be submitted as part of the VeDDRA consultation for consideration at the next annual review using the templates available in the call for comments.

19. Product defects

No additional guidance.

20. Psychological disorders

No additional guidance.

21. Renal and urinary disorders

No additional guidance.

22. Reproductive system disorders

No additional guidance.

23. Respiratory tract disorders

23.1. Panting, stridor and rale

'Panting' describes a fast and shallow open-mouthed breathing pattern observed commonly, but not exclusively, in dogs in response to both physiological and psychological disturbances. Since VeDDRA terms can only appear under one SOC, if it is considered that a report of panting indicates some form of anxiety, this should be coded separately.

'Stridor' is an abnormal, high-pitched sound produced by turbulent airflow through a partially obstructed airway within the upper respiratory tract. Its aetiology is therefore quite different from 'Rale', an abnormal rattling sound from within the chest and can be either bronchial or tracheal. This is reflected in their coding where cross referencing has also been provided.

SOC	HLT	PT	LLT
Respiratory tract disorders	Bronchial and lung disorders	Tachypnoea	Panting
Respiratory tract disorders	Bronchial and lung disorders	Rale	Bronchial rale
Respiratory tract disorders	Bronchial and lung disorders	Rale	Harsh lung sounds
Respiratory tract disorders	Bronchial and lung disorders	Rale	Increased lung sounds
Respiratory tract disorders	Tracheal and laryngeal disorders	Tracheal and laryngeal disorder NOS	Tracheal rales
Respiratory tract disorders	Respiratory tract disorders	Respiratory tract disorder NOS	Stridor (Upper respiratory; for lower respiratory see also Bronchial rale)

24. Skin and appendages disorders

No additional guidance.

25. Systemic disorders

25.1. Death

Death should always be recorded using VeDDRA. There are 8 choices at LLT level, all of which are described as 'Death' at PT level.

SOC	HLT	PT	LLT
Systemic disorders	Death	Death	Death
Systemic disorders	Death	Death	Death by euthanasia
Systemic disorders	Death	Death	Found dead
Systemic disorders	Death	Death	Increased culls
Systemic disorders	Death	Death	Increased mortality rate
Systemic disorders	Death	Death	Sudden death
Systemic disorders	Death	Death	Unexplained death
Systemic disorders	Death	Death	Unrelated death

This means that data extracted at PT level will not identify the relationship between the death and the adverse event so the case narrative must include all relevant details, including information as to how death occurred or why euthanasia was carried out if appropriate. The LLT 'Unrelated death' should be

used only when there is clear evidence that the death was not associated with the adverse event e.g. road accidents. It should not be used when the owner elected for euthanasia for economic reasons or due to an underlying disease, in which case the LLT 'Death by euthanasia' should be used. The LLT 'Sudden death' should be used when the fatality occurred unexpectedly e.g. without preceding clinical signs.

While there may be events involving multiple animals where it is appropriate to add both 'Death' and 'Death by euthanasia', it is important to be aware that the frequency of term selection in individual reports could influence the results of analysis, depending on the level at which analysis is carried out. Although the VICH standard enables the number of animals per VeDDRA term to be specified in individual reports, in cases where animals are euthanised (slaughtered) in high numbers, the LLT 'Increased culls' should be used.

See also section 25.3 Lack of efficacy for coding death in events following the use of euthanasia products. It should be noted that coding 'Unrelated death' is not necessary for reports of lack of efficacy to endo-parasitic products where parasites are identified following routine slaughter or for residue reports where product residues are detected following routine slaughter.

25.2. Planned euthanasia

'Planned euthanasia' should only be used in instances where euthanasia or slaughter is scheduled in advance, independently of the treatment administered or of an animal reacting, such as the following examples:

- when euthanasia is included in a clinical trial protocol;
- when production animals are scheduled for routine slaughter independently of the treatment administered.

This should not include welfare euthanasia even if planned.

It should be noted that 'Planned euthanasia' codes up to its own PT term of 'Planned euthanasia' and will not be included under the PT of 'Death'.

25.3. Lack of efficacy

If the reported adverse event clearly relates solely to lack of expected efficacy, the term 'Lack of efficacy' should be used in isolation without any of the observed signs indicative of the lack of efficacy. For any reports resulting in fatalities, 'Death' should also be coded. The term 'Uncoded sign' should never be used to code for the disease being treated.

If the report describes clinical signs relating to both safety and lack of expected efficacy or if there is any doubt as to what type of case it is (e.g. if clinical signs appear to have worsened following treatment) it should be submitted as one combined report with all signs being coded including 'Lack of efficacy'.

In order to provide further coding detail for multi-indication products e.g. combination antiparasitic products and multivalent vaccines, additional LLTs have been created, all situated within the PT 'Lack of efficacy'.

Lack of efficacy LLTs are now grouped together using the following system to aid user coding: Lack of efficacy (bacteria), Lack of efficacy (ectoparasite), Lack of efficacy (endoparasite), Lack of efficacy (fungi), Lack of efficacy (mycoplasma), Lack of efficacy (protozoa) and Lack of efficacy (virus).

Lack of expected efficacy following the use of euthanasia products should be coded using only the VeDDRA low level terms 'Lack of efficacy' and 'Unrelated death' (as the death was unrelated to the adverse event 'Lack of efficacy'). No other clinical signs observed should be coded using VeDDRA. In all cases, however, such reports are considered serious adverse events and should be reported accordingly.

25.4. Suspected infectious agent transmission, suspected reversal to virulence, suspected transmission of a vaccine strain, suspected recombination of a vaccine strain and suspected prolonged shedding of a vaccine strain

If a report of **suspected transmission of an infectious agent** via a VMP (e.g. contamination with a pathogen, insufficient inactivation etc.) is received, select the LLT 'Suspected infectious agent transmission'. Medical judgment should be used if the reporter does not explicitly state transmission of an infectious agent via a VMP but this could be implied by other data within the report.

In contrast to this term, **suspected reversal to virulence** concerns attenuated live vaccines, where clinical signs after administration indicate that the vaccine strain has reverted to be more pathogenic.

The term **suspected transmission of a vaccine strain** should be used in cases where unvaccinated animals acquire the vaccine strain, with or without signs of disease.

The term **suspected recombination of a vaccine strain** is related to cases in which a vaccine strain is suspected of recombination with another field strain and/or vaccine strain, as a specific genetic event, with or without signs of disease.

The term **suspected prolonged shedding of a vaccine strain** could be used in case of prolonged shedding or dissemination of a vaccine strain for a longer time-frame then that known for the vaccine strain i.e. as specified in the in the marketing authorisation application, European public assessment report (EPAR) or the product information (PI).

Medical judgment should be used to differentiate between these terms. As the determination of a relationship to a vaccine strain (i.e. vaccine strain, recombination) is different for each type of infectious pathogen, any suspicion of one of these terms should be based on a scientific approach that is based on characteristics of the suspected infectious pathogen and the reported measures completed in the event.

Some examples as aid have been provided below:

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	Suspected infectious agent transmission	Suspected infectious agent transmission
Systemic disorders	General signs or symptoms	Suspected recombination of a vaccine strain	Suspected recombination of a vaccine strain
Systemic disorders	General signs or symptoms	Suspected prolonged shedding of a vaccine strain	Suspected prolonged shedding of a vaccine strain
Systemic disorders	General signs or symptoms	Suspected reversal to virulence	Suspected reversal to virulence
Systemic disorders	General signs or symptoms	Suspected transmission of vaccine strain	Suspected transmission of vaccine strain

Examples:

Reported	LLT selected
A dog was treated with a nasal spray product and later developed a severe acute nasal infection with Bacteria X. Cultures of unopened containers of the nasal spray grew Bacteria X.	Suspected infectious agent transmission
Sows vaccinated with PRRS vaccine ABC. Clinical signs: premature births, mummification and stillborn piglets. PRRSV isolate found in affected piglets. Purification of isolate and subsequent sequencing of a sufficient amount of genome showed recombinant virus of ABC PRRSV vaccine strain with field PRRS vaccine strain XYZ.	Suspected recombination of vaccine strain
In a swine herd, piglets aged 3-18 weeks were vaccinated with a live attenuated vaccine virus. There were no associated reproductive problems in the herd at that time. 1-2 months later, there was an increased number of abortions and weak or stillborn piglets. Virus was isolated from weak or stillborn piglets and was further characterised as having originated from the live vaccine virus, causing suspicion of the live attenuated vaccine virus to have changed genetically and reverted to virulence under field conditions and started to spread within the herd, including to non-vaccinated sows.	Suspected reversal to virulence
In a poultry flock vaccinated with a live Salmonella vaccine, the vaccine strain is identified in unvaccinated animals and/or fomites (i.e. litter) and/or foodstuffs (eggs) for a longer period then that stated in the product information.	Suspected prolonged shedding of vaccine strain
Several possible scenarios: a) In a sheep flock vaccinated with *B. melitensis* Rev 1 live vaccine (in 3-6 months aged), the Rev 1 vaccine strain is detected from female dogs on the same farm. b) Sows vaccinated with a PRRS vaccine ABC prior to farrowing – clinical signs in piglets. XYZ PRRS vaccine virus found with 98% homology in ORF5; XYZ PRRS vaccine was never used on the farm;	Suspected transmission of a vaccine strain

26. Guidance relevant to multiple SOCs

26.1. Not otherwise specified (NOS) - New

LLTs involving 'not otherwise specified' (NOS) should only be chosen when a more specific LLT is not available for coding.

26.2. Anorexia

Anorexia in humans may be a symptom of a psychological disturbance, in which case the LLT 'Eating disorder NOS' in the SOC 'Psychological disorders' should be used. This term should be used only for human reports.

SOC	HLT	PT	LLT
Psychological disorders	Eating disorders	Eating disorder NOS	Eating disorder NOS (see Systemic for anorexia etc)

Anorexia is frequently used by reporters to describe loss of appetite as a clinical sign in many different types of adverse reaction in animals and humans. In this situation a term from the PT 'Anorexia' in the SOC 'Systemic disorders' should be selected (see examples below).

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	Anorexia	Anorexia
Systemic disorders	General signs or symptoms	Anorexia	Decreased appetite
Systemic disorders	General signs or symptoms	Anorexia	Reduced food intake

26.3. Collapse

There are three LLT terms available in VeDDRA to describe collapse, each of which is located in a different SOC (see below). It is important to ensure that the choice of term at LLT level is appropriate in the context of the overall reaction. None of the LLT terms describing collapse are in the SOC 'Immune system disorders', yet this clinical sign is often reported in association with anaphylaxis (see section 10.1).

SOC	HLT	PT	LLT
Cardio-vascular system	Circulatory disorders	Circulatory shock	Circulatory collapse (see also Neurological and Systemic disorders)
Neurological disorders	Impaired consciousness	Loss of consciousness	Collapse (see also Cardio-vascular and Systemic disorders)

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	Collapse NOS	Collapse NOS (see also Cardio-vascular and Neurological disorders)

26.4. Decubitus and decubitus ulceration

The LLT term 'Decubitus' which maps to the PT term 'Recumbency' describes the body position of the animal. Ulceration (or decubitus ulceration as it is sometimes referred) due to prolonged recumbency should be coded using the term 'Skin ulceration'.

26.5. Dullness, lethargy, sleepiness, drowsiness, depression and malaise

Reporters often describe an animal which is ill in non-specific terms. The clinical signs which are reported should be viewed in the context of the overall reaction and it is important to be aware of the SOC in which an individual LLT is located. An exact match at LLT level could exaggerate the seriousness of the reaction. For example, dullness is frequently used to describe a mild, transient post-vaccinal reaction, but at LLT level the term is located in the SOC 'Neurological disorders' which does not reflect the true nature of the reaction. In this case it is important to record any additional reported clinical signs which give a more accurate picture of the overall reaction. If dullness is the only clinical sign which is reported, it may be necessary to obtain more details from the reporter.

Similarly, although the terms sleepiness and drowsiness may be used interchangeably by reporters in cases where there is either neurological impairment or general lethargy, from the overall picture of the report, it should be possible to select the most appropriate term from the list in the following table:

SOC	HLT	PT	LLT
Neurological disorders	Impaired consciousness	Impaired consciousness	Dullness
Neurological disorders	Impaired consciousness	Somnolence	Sleepiness – neurological disorder
Neurological disorders	Mental impairment	Cognitive disorder NOS	Drowsiness – neurological disorder
Systemic disorders	General signs or symptoms	Lethargy	Lethargy (see also Central nervous system depression in Neurological)
Systemic disorders	General signs or symptoms	Lethargy	Depression
Systemic disorders	General signs or symptoms	Lethargy	Dull
Systemic disorders	General signs or symptoms	Lethargy	Drowsiness – systemic disorder

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	Lethargy	Sleepiness – systemic disorder
Systemic disorders	General signs or symptoms	Lethargy	Mopey
Systemic disorders	General signs or symptoms	Malaise	Malaise
Systemic disorders	General signs or symptoms	Malaise	Off colour

26.6. Embolism and thromboembolism - Updated

Since emboli are generally formed in the heart, this LLT is found under the PT 'Cardiovascular embolism'.

SOC	HLT	PT	LLT
Cardio-vascular system disorders	Cardiac/heart disorders	Cardiovascular embolism	Aortic thromboembolism
Cardio-vascular system disorders	Cardiac/heart disorders	Cardiovascular embolism	Cardiac embolism
Cardio-vascular system disorders	Cardiac/heart disorders	Cardiovascular embolism	Cardiovascular embolism
Cardio-vascular system disorders	Cardiac/heart disorders	Cardiovascular embolism	Embolism
Cardio-vascular system disorders	Cardiac/heart disorders	Cardiovascular embolism	Fibrocartilaginous embolism (FCE)
Cardio-vascular system disorders	Cardiac/heart disorders	Cardiovascular embolism	Pulmonary thromboembolism

26.7. Foaming at the mouth

There are two LLT terms available in VeDDRA to describe the drooling of non-bloody fluid from the mouth of an animal which is often described by reporters as 'Foaming at the mouth'. An additional term exists to describe incidents when bloody foam is seen in both the mouth and nose.

SOC	HLT	PT	LLT
Digestive tract disorders	Oral cavity disorders	Hypersalivation	Foaming at the mouth
Respiratory tract disorders	Respiratory tract disorders	Foam in respiratory tract	Foam in the mouth

SOC	HLT	PT	LLT
Respiratory tract disorders	Respiratory tract disorders	Foam in respiratory tract	Bloody foam in mouth and nose

As the terms are in different SOCs, their selection at LLT level could be critical in ensuring that the clinical syndrome described by the reporter is recorded correctly. It is advisable to include additional LLT terms from the relevant SOCs whenever possible, so that the adverse reaction is characterised accurately. It should also be remembered that 'Foaming at the mouth' can be associated with neurological disorders such as muscle tremors, convulsions and tetany, although in these cases it is unlikely to be the sole clinical sign which is reported.

26.8. Head tilt, balance problems and ataxia

Head tilt may be reported in association with adverse reactions which did not result from the administration of a product into the ear. The choice of this term at LLT level can be difficult as it may be due to either inner ear or neurological causes. The usual default would be to select the term 'Head tilt – ear disorder', but in situations where the overall picture is one of a neurological disturbance, the alternative 'Head tilt – neurological disorder' should be selected. Conversely, balance problems may be vestibular in origin, so when they are reported in association with a possible ear disorder, a term from the SOC 'Ear and labyrinth disorders' should be included with terms from the SOC 'Neurological disorders'.

SOC	HLT	PT	LLT
Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Head tilt – ear disorder
Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Internal ear disorder
Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Tumbling circling disease (see also Ataxia in Neurological)
Ear and labyrinth disorders	Internal ear disorders	Internal ear disorder	Vestibular disorder NOS
Neurological disorders	Central nervous system disorders	Central nervous system disorder NOS	Head tilt – neurological disorder
Neurological disorders	Coordination and balance signs	Ataxia	Balance impaired
Neurological disorders	Coordination and balance signs	Ataxia	Balance problem
Neurological disorders	Coordination and balance signs	Ataxia	Equilibrium disorder
Neurological disorders	Coordination and balance signs	Ataxia	Lack of coordination (see also Ear – vestibular disorder)

26.9. Hyperactivity

In animals, hyperactivity is regarded as a behavioural disorder in VeDDRA. This term should be used only for animal reports.

SOC	HLT	PT	LLT
Behavioural disorders	Other behavioural disorders	Hyperactivity	Hyperactivity

Hyperactivity may also be reported in a human as a symptom of abnormal behaviour, in which case the LLT 'Hyperactive' in the SOC 'Psychological disorders' should be used. This term should be used only for human reports.

SOC	HLT	PT	LLT
Psychological disorders	Personality and mood disorders	Abnormal behaviour	Hyperactive

26.10. Local reactions

Adverse reactions which occur at the application, injection or implantation site should be described using LLT terms selected from the appropriate HLT under SOC 'Application site disorders'. This distinguishes them from non-specific local reactions which may be more difficult to assess for causality. For example:

SOC	HLT	PT	LLT
Application site disorders	Injection site reactions	Injection site alopecia	Injection site alopecia
Skin and appendages disorders	Hair follicle and sebaceous gland disorders	Alopecia	Alopecia local

26.11. Pain and discomfort

Animals are sometimes reported as being in pain or showing signs of pain when touched. This could reflect a systemic condition, in which case the choice of one of the following LLT terms in the SOC 'Systemic disorders' would be appropriate. However, an exaggerated response could be a sign of a different syndrome. A separate PT exists for cases where discomfort, as opposed to overt pain, is reported.

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	General pain	General pain (see other SOCs for specific pain)
Systemic disorders	General signs or symptoms	General pain	Pain NOS
Systemic disorders	General signs or symptoms	Localised pain NOS	Localised pain NOS (see other SOCs for specific pain)

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	Discomfort NOS	Discomfort NOS
Systemic disorders	General signs or symptoms	Discomfort NOS	Uncomfortable
Neurological disorders	Sensory abnormalities	Hyperaesthesia	Hypersensitivity to pain

26.12. Product defects and counterfeits

SOC	HLT	PT	LLT
Other event	Other event	Counterfeit product	Confirmed counterfeit product
Other event	Other event	Counterfeit product	Suspect counterfeit product
Product defects	Product defect NOS	Product defect NOS	Product defect NOS

'Product defect NOS' should be used when an adverse event is reported in relation to any of the following situations:

a) If the veterinary medicinal product (i.e. finished dosage form e.g. tablet, capsule, solution) is suspected to be abnormal (e.g. murky instead of clear, unknown sediments, abnormal viscosity, abnormal smell, potency issues, contamination, etc.);

b) In circumstances where there is another defect which is not related to a product quality issue (e.g. defective packaging, defective primary containers, issues with labelling, missing tablets, underfilling, etc.); or

c) Administration device issues that relate to a defect (e.g. missing or broken, incorrect calibration, calibration illegible). If, however there are problems with the use of the administration device (e.g. device difficult to use) please refer to specific terms under SOC 'Medication and product use errors'.

26.13. Prolonged anaesthesia, premature anaesthesia recovery and rough recovery

Although 'Prolonged anaesthesia' and 'Premature anaesthesia recovery' might on the face of it be considered simply the opposite of each other they are in quite different SOCs, as indicated below. A separate PT exists for 'Rough recovery' and therefore this should also be coded when applicable.

SOC	HLT	PT	LLT
Neurological disorders	Impaired consciousness	Sedation	Prolonged anaesthesia
Systemic disorders	General signs or symptoms	Premature anaesthesia recovery	Premature anaesthesia recovery
Systemic disorders	General signs or symptoms	Rough recovery	Rough recovery

26.14. Recumbency, prostration and self-auscultation position

Recumbency can be the result of several different types of adverse reaction and the term is in the SOC 'Systemic disorders', under the PT 'Recumbency'. Some abnormal postures relating to recumbent animals can also be found as LLTs within this PT, including 'Prostration' (a specific body position where the animal is lying completely flat out) and 'Self-auscultation position' (when the animal's neck is bent so that the head lies against the chest).

In situations where the reason for recumbency could be neurological, it would be advisable to select at least one other LLT term from the SOC 'Neurological disorders' (see examples below) in order to capture this information.

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	Recumbency	Abnormal posture
Systemic disorders	General signs or symptoms	Recumbency	Lateral recumbency
Systemic disorders	General signs or symptoms	Recumbency	Prostration
Systemic disorders	General signs or symptoms	Recumbency	Recumbency
Systemic disorders	General signs or symptoms	Recumbency	Self auscultation position
Systemic disorders	General signs or symptoms	Recumbency	Unable to rise
Neurological disorders	Paralytic and paretic disorders	Paralysis	Hind limb paralysis
Neurological disorders	Paralytic and paretic disorders	Paresis	Paresis
Neurological disorders	Coordination and balance signs	Ataxia	Unable to stand

26.15. Reduced urination

Failure to urinate may be due to either a physiological or anatomical problem within the urinary tract itself or else a more psychological or behavioural response (e.g. to distress or fear). A complete absence of urination should be coded as 'Anuria' unless there is evidence of behavioural dysfunction in which case the term 'Not urinating' can be selected. Note also the terms in the PTs 'Dysuria' and 'Stranguria', which represent difficulty or pain in urinating respectively.

SOC	HLT	PT	LLT
Behavioural disorders	Other behavioural disorders	Inappropriate urination	Not urinating
Renal and urinary disorders	Renal disorders	Anuria	Anuria
Renal and urinary disorders	Urinary tract disorders	Dysuria	Difficulty in micturition
Renal and urinary disorders	Urinary bladder disorders	Polyuria/pollakiuria	Pollakiuria
Renal and urinary disorders	Urinary tract disorders	Stranguria	Painful urination

26.16. Reluctance to move

Non-specific changes in an animal's behaviour, such as inertia, are difficult to record accurately if other clinical signs are not reported. There are several choices at LLT level (see below). In cases where the situation is unclear, and few details are reported it would be advisable to select a term in the PT 'Lethargy' in order to indicate the generalised systemic nature of the reaction. This could be important in a situation where an animal is showing some signs of mobility but not the full range of movement. In such cases a single term from the SOC 'Musculoskeletal disorders' or the SOC 'Neurological disorders' may not be an accurate description of the reaction.

SOC	HLT	PT	LLT
Systemic disorders	General signs or symptoms	Reluctant to move	Reluctant to move
Musculoskeletal disorders	Musculoskeletal disorders	Musculoskeletal disorder NOS	Limb weakness
Neurological disorders	Coordination and balance signs	Ataxia	Walking difficulty

26.17. Shaking, shivering or trembling

In many instances a patient may be reported to be shaking, shivering, or trembling. These signs are non-specific and may be associated with neurological causes or other systemic causes such as fever, fear, pain, etc. When the signs are correlated or consistent with a neurological event, the appropriate LLT linking to a 'Neurological disorders' SOC should be selected. If the case narrative clearly indicates a

non-neurological cause, the LLT 'Shaking, shivering or trembling (non-neurological)' in the 'Systemic disorders' SOC should be selected and this should be clarified in the adverse event report narrative. If the underlying cause of the signs is unclear, the appropriate LLT from the 'Neurological disorders' SOC should be selected, by default.