Questions and answers on serious non-fatal adverse events and reporting rules

This questions and answers document was developed to enable all stakeholders understand what constitutes a serious non-fatal adverse event following use of a veterinary medicinal product (VMP), after recommended or non-recommended use. The document provides guidance on which clinical signs or events should be considered as life-threatening or should be considered as resulting in persistent or significant disability or incapacity or congenital anomaly or birth defect. Some clinical signs may vary according to species. This questions and answers document also provides information on serious adverse event reporting, and complements the guidance included in Volume 9B of The Rules Governing Medicinal Products in the European Union – Guidelines on Pharmacovigilance for Medicinal Products for Veterinary Use.

1. **What is life-threatening in the context of a serious adverse event?**

A life threatening adverse event is one in which the animal was at risk of death at the time of the event.

2. **What is persistent or significant disability in this context?**

Disability in this context occurs when an animal or group of animals is unable to accomplish elementary every-day activities. Significant disability also occurs in cases when a veterinarian considers it necessary to administer VMPs that would not normally be used as a treatment of first choice e.g. corticosteroids in order to stop escalation or worsening of clinical signs. Even if treatment is successful and clinical signs of the adverse event are not exacerbated or do not last long, this will also be considered as significant disability.

3. **How should (fatal and non-fatal) serious adverse events be reported?**

Serious fatal or non-fatal adverse events should be reported in an expedited manner, regardless of the causality assessment.
4. **What are the examples of serious non-fatal adverse events?**

   a. There are clinical signs that should **automatically** lead to classification as serious adverse events as soon as they are reported, regardless of the causality assessment, the outcome, the time to onset etc. (= if it is mentioned, then the adverse event is serious).

   Some examples are provided below, however please note that this list is not exhaustive:
   - shock (all shock reactions, whatever the origin is: circulatory, anaphylactic etc.). Clinical signs of anaphylaxis may vary according to species. For anaphylactic shock, see Table 1;
   - respiratory distress, dyspnoea, apnoea;
   - collapse, syncope;
   - convulsions/seizures (even if first occurrence);
   - blindness/impaired vision (also temporary);
   - deafness/impaired hearing (also temporary);
   - paralysis, paresis;
   - failure of vital organs (total loss of function);
   - uterine haemorrhage, uterine rupture, or pyometra;
   - ovariohysterectomy or caesarean section/dystocia following lack of expected efficacy (LEE) (e.g. after administration of abortifacient agent);
   - peritonitis;
   - diabetes mellitus;
   - severe fish body deformities;
   - malignant neoplasia (including sarcomas at administration sites);
   - stillbirth, abortion, congenital anomaly or birth defect (excluding dew claws);
   - LEE during euthanasia or anaesthesia;
   - recumbency in large animals.

   b. Clinical signs or reactions that could be considered serious or non-serious depending on other **criteria** such as:
   - systemic sequelae;
   - duration;
   - depth, extent, localisation of lesions;
   - physiological context (age of the animal, gestation etc.).
   - Any other information that could make the assessor think that what is reported in the adverse event is a life-threatening situation, or a persistent or significant disability/incapacity.
Here are some examples:

- facial oedema/angioedema or Quincke’s oedema: consider if dyspnoea is associated or if serious oedema has also been detected (pulmonary, laryngeal etc.);
- metabolic and/or endocrinological disorders (elevated renal parameters or liver enzymes etc.): clinical importance has to be considered;
- haematological disorders: clinical importance has to be considered;
- cardiac arrhythmia: consider clinical importance (collapse, fatigue etc.);
- gastro-enteritis;
- recumbency: consider duration, species;
- anorexia: consider duration, species (e.g. guinea pigs, rabbits) and consider systemic sequelae;
- reduced mobility (lameness, decubitus): systemic signs, duration, species to be considered (see also recumbency in large animals in 4a above);
- injection and application site reactions: systemic signs, localisation, depth and extent of lesions and/or reduced mobility to be considered;
- acute mastitis with systemic signs or recumbency;
- metritis;
- dermatological signs of hypersensitivity reaction (toxic epidermal necrolysis (TEN), Steven-Johnson-syndrome, lupoid onychodystrophy);
- photosensitisation: systemic signs, localisation, depth and extent of lesions to be considered;
- pemphigus foliaceous: systemic signs, localisation, depth and extent of lesions to be considered;
- pancreatitis: systemic signs to be considered;
- significant reduction in physiological function occurring and lasting for a longer period e.g. reduced milk yield, reduced egg production, reduced growth rate;
- lack of expected efficacy (LEE): if the LEE results in a life-threatening condition (e.g. cluster seizures in epileptic dogs) or in persistent or significant disability/incapacity of the animal or the group of animals.
Table 1 Clinical signs of anaphylactic shock reactions in different species

Anaphylactic shock is an acute allergic, potentially life-threatening, Type 1 hypersensitivity reaction resulting from the generalised release of potent vasoactive substances from mast cells and basophils. The clinical signs of anaphylaxis can vary depending on the major so-called “shock organ” relevant to the species. The table below summarises the differences between species, however this list is not exhaustive.

<table>
<thead>
<tr>
<th>Species</th>
<th>Major shock organ(s)</th>
<th>Pathology</th>
<th>Clinical signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dogs</td>
<td>Liver</td>
<td>Hepatic and intestinal engorgement, visceral haemorrhage.</td>
<td>Initially excitement, urticaria, angioedema and pruritus, then vomiting and defecation. Finally collapse, dyspnoea and convulsions.</td>
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<tr>
<td>Cats</td>
<td>Respiratory tract</td>
<td>Bronchoconstriction, pulmonary haemorrhage, oedema and emphysema, oedema of the glottis.</td>
<td>Initially angioedema and pruritus around the face, then salivation, dyspnoea, vomiting, incoordination and collapse.</td>
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<tr>
<td></td>
<td>Gastrointestinal tract</td>
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<tr>
<td>Horses</td>
<td>Respiratory tract</td>
<td>Pulmonary oedema and emphysema, intestinal oedema and haemorrhage.</td>
<td>Initially shivering, sweating and incoordination. Possibly coughing, dyspnoea and diarrhoea. Finally collapse. Colic.</td>
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<tr>
<td></td>
<td>Gastrointestinal tract</td>
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<tr>
<td>Cattle and sheep</td>
<td>Respiratory tract</td>
<td>Pulmonary haemorrhage, oedema and emphysema.</td>
<td>Initially urticaria, angioedema, pruritus and restlessness. Coughing, severe dyspnoea and cyanosis. Also defecation, urination, bloat and collapse.</td>
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<tr>
<td></td>
<td>Gastrointestinal tract</td>
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<tr>
<td>Pigs</td>
<td>Respiratory tract</td>
<td>Pulmonary oedema and emphysema, intestinal oedema and haemorrhage.</td>
<td>Dyspnoea, cyanosis, pruritus and collapse.</td>
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<td></td>
<td>Gastrointestinal tract</td>
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</tbody>
</table>

5. References
