



Veterinary Medicines Guidance Note

Marketing Authorisations for Veterinary Medicinal Products - Supplementary Guidance on Pharmacovigilance

DRAFT

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ASSURING THE SAFETY, QUALITY AND EFFICACY
OF VETERINARY MEDICINES



THESE NOTES ARE ONLY A GENERAL GUIDE AND MUST NOT BE TREATED AS A COMPLETE OR AUTHORITATIVE STATEMENT OF THE LAW ON ANY PARTICULAR CASE

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INTRODUCTION

1. This is one of a series of Veterinary Medicines Guidance (VMG) Notes explaining requirements under the Veterinary Medicines Regulations ('the Regulations'). The Regulations are revoked and replaced every year, so the references to them should be read as referring to the ones that are currently in force. Therefore, the date and number of the Statutory Instrument are not shown in this VMG Note. The VMG Notes will be updated as necessary and the date of the most recent update is shown on the front cover.
2. The Regulations set out the UK controls on veterinary medicines, including their manufacture, advertising, marketing, supply and administration. VMG Note 1: *An Introduction to Marketing Controls on Veterinary Medicines* provides basic information about the scope of the Regulations and the requirement for Marketing Authorisations (MAs) is given in. This note concerns the provisions for pharmacovigilance – the monitoring of suspected adverse reactions (SARs) to veterinary medicines and related matters - in the UK. Further information on pharmacovigilance, including forms for reporting SARs, is available on the VMD website (www.vmd.gov.uk) under General Information, Adverse Reactions.
3. Under the Regulations failure to comply with the pharmacovigilance requirements is an offence. As the competent authority in the UK, the Veterinary Medicines Directorate (VMD) discharges its pharmacovigilance responsibilities through the Suspected Adverse Reaction Surveillance Scheme (SARSS). The Scheme monitors suspected adverse reactions to veterinary medicinal products in all animal species and in humans.
4. Guidance on pharmacovigilance is published by the European Commission in *The rules governing medicinal products in the European Union, Volume 9 – Pharmacovigilance*. This and other volumes in the same series are available on the Commission website (<http://pharmacos.eudra.org/F2/eudralex/index.htm>) or in print from The Stationery Office Ltd or from the Office for Official Publications of the European Communities in Luxembourg (http://publications.europa.eu/index_en.htm). Part of the Commission guidance is also available as a separate guidance note produced by the EU Committee for Veterinary Medicinal Products (CVMP) and is available from the European Medicines Agency (www.emea.eu.int). This VMG Note is intended to supplement the European Commission guidance and should be read with it.

WHERE TO SEND REPORTS

5. Reports for all SARs occurring within the UK should be sent to the VMD SARSS team at the following address:

Veterinary Medicines Directorate
FREEPOST KT 4503
Woodham Lane
New Haw

Addlestone
Surrey, KT15 3BR

6. The Regulations primarily place reporting obligations on marketing authorisation holders (MAHs).
7. Different types of reaction are defined as follows:
 - “Human adverse reaction” means a reaction that is noxious and unintended and that occurs in a human being following exposure to a veterinary medicine.
 - “Serious adverse reaction” means an adverse reaction that:
 - results in death;
 - is life-threatening;
 - results in significant disability or incapacity;
 - is a congenital anomaly/birth defect;
 - results in permanent or prolonged signs in the animals treated.
 - “Unexpected adverse reaction” means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of the product characteristics (SPC).

PHARMACOVIGILANCE QUALIFIED PERSON (PQP)

8. Each MAH is required to have permanently and continuously at their disposal an appropriately qualified person responsible for pharmacovigilance. The VMD considers that any person who is capable of competently performing the specified duties would meet the requirement. All applications for national MAs have to be accompanied by the name and contact details of a PQP. VMG Note 20 – *Veterinary Medicinal Products – Qualified Persons* contains further details on what is required of a PQP.

REPORTING REQUIREMENTS

SERIOUS SAR REPORTS IN ANIMALS

9. The Regulations require MAHs to record all serious SARs to their products of which they become aware and to report them to the VMD within 15 days. All serious SARs, including those arising from off-label use or misuse, should be reported. Reports should be made electronically if this is possible.
10. Advice on the interpretation of “serious adverse reaction” is given in the Commission guidance. However, this provides only very broad guidance on non-fatal adverse reactions which are clinically serious and which should be reported to the VMD in the judgement of the company assessor. The SARSS

team should be consulted, or a report submitted as for a serious SAR, if doubt exists as to whether or not a reaction is serious. Examples illustrating the VMD's view of what constitutes a non-fatal serious SAR are given in Annex 1.

11. In addition to a narrative description of the suspected adverse reaction, all reports of serious SARs should include a causality assessment using the "ABON" code (A - probable, B - possible, O - insufficient data, N - not likely). A list of presenting signs should also be included, using terminology from the Veterinary Dictionary for Drug Regulatory Activities (VEDDRA), available on the VEDDRA website (www.veddra.org).

SARs OCCURRING IN THE EU

12. The Commission guidance explains that MAHs should report details of all serious SARs occurring within the Community to the Member State in whose territory the incident occurred. The VMD considers that Member States' national pharmacovigilance centres should assess and, if appropriate, further investigate SARs occurring within their territory, as they are likely to be familiar with local conditions. The VMD will therefore only consider SARs in other Member States that have been reported by the relevant pharmacovigilance centre and will not request SAR reports for other Member States from MAHs.

SARs OCCURRING OUTSIDE THE EU (THIRD COUNTRY REPORTS)

13. Serious unexpected SARs in animals and suspected human adverse reactions involving products authorised in the UK should be reported to the VMD within 15 days. The following points should be taken into consideration when reporting third country SARs:
 - any disparities between the UK summary of the product characteristics (SPC) and that of the country where the SAR occurred;
 - the precise identity, formulation and strength of the product involved;
 - the causality assessment.

HUMAN REACTIONS TO VETERINARY MEDICINES

14. Any report of SARs in humans should include:
 - details about the person who experienced the adverse reaction and the VMP involved,
 - details of the nature and duration of the exposure to the product; and
 - information about the method of its administration and the animals being treated.

The occupation or status of the person should also be reported if it is relevant to the exposure, for example a veterinary surgeon, farm worker or pet owner. If it is at all possible, MAHs should obtain the name of the person who experienced the SAR. If this is not possible, as may be the case when doctors report direct to the MAH, the initials of the patient should be recorded and, if known, the town and

county of their address. Alternatively a reference should be provided so that follow-up action can be taken if required.

15. The Commission guidelines provide for other aspects of pharmacovigilance in addition to adverse reactions occurring in animals and humans. These are:
 - lack of expected efficacy;
 - off-label use/misuse;
 - reported violations of approved residue limits;
 - environmental problems.

SUSPECTED LACK OF EXPECTED EFFICACY

16. If an authorised product fails to have the recognised effect in an animal, it should be reported as a suspected lack of expected efficacy. The assessment of suspected lack of expected efficacy should take the following points into consideration:
 - accuracy of diagnosis;
 - the claims authorised for the product;
 - the storage and handling of the product;
 - whether the product was used in accordance with the manufacturer's instructions;
 - other factors such as hygiene at the time of administration, the influence of stress from handling, and the possibility of immunosuppression.
17. Suspected lack of expected efficacy which may indicate a defect in the product or batch should be reported to the SARSS team immediately.
18. Incidents involving suspected lack of expected efficacy should normally be reported in the Periodic Safety Update Report (PSUR). However, the Commission guidance provides for incidents to be reported within 15 days in certain specific circumstances. The VMD considers these circumstances to include a lack of efficacy associated with the possible development of antimicrobial or anthelmintic resistance.

OFF-LABEL USE/MISUSE

19. Off-label use is the use of a VMP that is not in accordance with the SPC and includes misuse and abuse of the product. SARs arising as a result of such use should be recorded in the PSUR and be clearly identified as off-label use or misuse. Cases involving death or which are otherwise considered to be serious should be reported within 15 days, as for other serious SARs.

VALIDITY OF WITHDRAWAL PERIODS

20. The VMD should be informed of any cases where residues of an authorised veterinary medicine in tissues or food products of treated food-producing animals

cast doubt on the validity of the withdrawal period of the veterinary medicine concerned.

21. Such reports may arise from a number of different sources, for example:
 - reports of incidents from farmers or veterinary surgeons, e.g. residues in animal milk found through bulk milk tank screening tests;
 - reports by the State Veterinary Service following the investigation of residues incidents identified through statutory programmes of surveillance;
 - reports of individual incidents from public analysts or food producers who undertake the routine monitoring of foodstuffs;
 - reports from doctors or hospitals of cases of ill health in humans suspected of having been caused by residues in food.
22. Reports that cast doubt on the validity of withdrawal periods should normally be included in the relevant PSUR. However, incidents that could compromise food safety or public health should be recorded and reported immediately to the SARSS.

ENVIRONMENTAL PROBLEMS

23. The following advice is provided as an aid to the reporting of environmental incidents.
24. When an authorised veterinary medicine is alleged to have caused an environmental problem, the MAH should collect as much information as possible including:
 - identity of product, i.e. MA number;
 - batch number;
 - date of use of the product;
 - date when alleged environmental problem occurred;
 - details of reported problem;
 - likely route of contamination;
 - evidence that an environmental problem has occurred;
 - initial steps taken by the MA holder.
25. A report form (MLA 1) should be forwarded to the SARSS team as soon as possible after the above information has been collected.

PERIODIC SAFETY UPDATE REPORTS (PSURs)

26. Records of all SARs should be submitted in the form of a PSUR for each MA. Following the initial placing on the market, PSURs should be submitted immediately upon request or at the following intervals:
 - 6-monthly for the first 2 years,
 - annually for the subsequent 2 years,
 - thereafter, at three-yearly intervals.
27. If no SARs have been reported in the period of the PSUR, a nil report should be submitted.
28. Each SAR should include a company case reference number. SARs that have been reported to the MAH by the VMD, and others for which it is known, should include the VMD's ADR (Adverse Drug Reaction) number in addition to the company case reference.
29. Each SAR reported in a PSUR should be line-listed. A summary of each incident should be provided and all presenting signs listed using VEDDRA terminology. The conclusions and comments of the MAH should include a causality assessment using the ABON classification (see paragraph 10).
30. In addition to a scientific evaluation of the risk-benefit balance of the veterinary medicine, a PSUR should include the following:
 - the volume of the product sold in each year covered by the report, calculated on an annual basis beginning 1st January;
 - the number of adverse reactions for each year of the report;
 - the ratio of adverse reactions to volume of product sold, together with an explanation of the basis of the calculation;
 - differentiation of data based on:
 - target species (if the product is authorised for use in more than one species);
 - reaction type (such as serious, non-serious, human, suspected lack of expected efficacy, unauthorised use or other);
 - the country of origin of the report.
31. If the product is indicated for more than one species, the information listed above should be broken down by species, so far as is practicable based on the estimated conditions of use of the product. Data relating to different formulations (either different dosage forms or different strengths) should be provided in separate reports.

RELEASE OF INFORMATION BY THE MA HOLDER

32. Concerns arising from pharmacovigilance relating to the safety of a product for the target animal, operator, consumer or the environment should first be notified to the VMD before any information is made public. This includes notification or advice to veterinarians in the event of a product or batch defect, or the withdrawal of a product from the market for safety reasons. The VMD should also be informed of safety concerns resulting from quality issues.
33. It is not intended that this requirement should prevent or restrict the discussion of individual SARs with the people who reported them or who are otherwise involved with the cases.

FURTHER INFORMATION

34. Further information is available from the Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3LS - Tel: (+44) (01932) 336911, or Fax: (+44) (01932) 336618 or E-mail: VMGNotes@vmd.defra.gsi.gov.uk. Veterinary Medicines Guidance Notes and other information, including details of VMD contacts, are available on the VMD website (www.vmd.gov.uk).

ANNEX 1

Examples of Serious Non-Fatal SARs by Animal Species

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EXAMPLES OF SERIOUS NON-FATAL SUSPECTED ADVERSE REACTIONS BY ANIMAL SPECIES

The following are examples of non-fatal SARs which could be considered to be serious if they occurred in a time relationship with the administration of a veterinary medicine. The list is intended for guidance only.

GENERAL CONDITIONS

- Anaphylaxis occurring within a few hours. Clinical signs may vary according to species. See Table 1.
- Blindness (partial, temporary or permanent) in all species.
- Collapse occurring immediately and lasting longer than 10 minutes in all species.
- Convulsions and/or other neurological signs occurring within a few hours in all species.
- Sarcomas at administration sites in cats.
- Severe epileptic fits and lethargy occurring within a few hours in all species.
- Severe respiratory distress occurring immediately in all species.
- Severe pyrexia occurring immediately in all species.
- Severe photosensitisation occurring within a few days in cattle and sheep.
- Severe gastro-enteritis occurring within a few days in all species.
- Acute mastitis occurring within a few days in cattle and sheep.
- Acute metabolic disorders, hepatic or renal failure occurring within a few days in dogs and cats.
- Significant reduction in physiological function occurring within one week and lasting for a longer period, e.g. persistent anorexia, circulatory collapse, reduced milk yield, reduced egg production, reduced growth rate, anaemia, blood dyscrasias.
- Birth defects with sequelae, e.g. deafness or blindness, in all species.
- Fish body deformities.

Table 1 - Clinical signs of anaphylaxis in different species

Anaphylaxis is an acute, 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.

Species	Shock Organ(s)	Pathology	Clinical Signs
Dogs	Liver	Hepatic and intestinal engorgement, visceral haemorrhage.	Initially excitement, urticaria, angioedema and pruritus, then vomiting and defecation. Finally collapse, dyspnoea and convulsions.
Cats	Respiratory tract Gastrointestinal tract	Bronchoconstriction, pulmonary haemorrhage, oedema and emphysema, oedema of the glottis.	Initially angioedema and pruritus around the face, then salivation, dyspnoea, vomiting, incoordination and collapse.
Horses	Respiratory tract Gastrointestinal tract	Pulmonary oedema and emphysema, intestinal oedema and haemorrhage.	Initially shivering, sweating and incoordination. Possibly coughing, dyspnoea and diarrhoea. Finally collapse.
Cattle and sheep	Respiratory tract	Pulmonary haemorrhage, oedema and emphysema.	Initially urticaria, angioedema, pruritus and restlessness. Coughing, severe dyspnoea and cyanosis. Also defecation, urination and bloat.
Pigs	Respiratory tract Gastrointestinal tract	Pulmonary oedema and emphysema, intestinal oedema and haemorrhage.	Dyspnoea, cyanosis, pruritus and collapse.

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