Veterinary Medicines Directorate

Document Withdrawn as out of date. Please refer to guidance at Veterinary medicines guidance - GOV.UK

GUIDANCE ON THE USE OF CASCADE

Last updated July 2013

QUICK START GUIDE

This Veterinary Medicines Guidance Note (VMGN) is aimed primarily at veterinary surgeons and is intended to provide guidance on the application of the Cascade.

The quick start guide is a summary of the provisions of the Veterinary Medicines Regulations (VMR); detailed information is found in the body of the guidance note.

- The Cascade is a legislative provision in the VMR that allows a veterinary surgeon to prescribe unauthorised medicines that would not otherwise be permitted.

- The principle of the Cascade is that, if there is no suitable veterinary medicine authorised in the UK to treat a condition, the veterinary surgeon responsible for the animal may, in particular to avoid causing unacceptable suffering, treat the animal in accordance with the following sequence, in descending order of priority:

    - A veterinary medicine authorised in the UK for use in another animal species or for a different condition in the same species.

    - If there is no such product, the next option is either –
        - a medicine authorised in the UK for human use, or
        - a veterinary medicinal product (VMP) not authorised in the UK but authorised in another Member State (MS) for use in any animal species (in the case of a food-producing animal the medicine must be authorised in a food producing species) in accordance with an import certificate issued by the VMD.

    - If there is no such product, the last option is a medicine prescribed by the veterinary surgeon responsible for treating the animal and prepared extemporaneously by a veterinary surgeon, a pharmacist or a person holding an appropriate manufacturer's authorisation. In exceptional circumstances, medicines may be imported from Third countries through the VMD's import scheme.

Food producing animals may only be treated under the Cascade with medicines which contain pharmacologically active substances listed in the Table of Allowed Substances in Commission Regulation EU (European Union) No 37/2010, in the interest of food safety. EU Commission Regulation No 37/2010 can be found on
http://ec.europa.eu/health/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf

- A veterinary surgeon prescribing for, or administering a medicine to, food-producing animals under the Cascade is required to specify an appropriate withdrawal period to the animal produce. When setting the withdrawal period, a veterinary surgeon must take into account known information about the use of the product on the authorised species when prescribing to another species under the Cascade. Unless the medicine indicates a withdrawal period for the species concerned, this should not be less than:

    - 7 days for eggs and milk
    - 28 days for meat from poultry and mammals
    - 500 degree days for meat from fish

- For products imported from another MS under a Special Import Certificate (SIC), provided that the product is used strictly according to the terms of its EU authorisation, the withdrawal period applied should be the period stated on the EU product literature. For products imported under an SIC and used in a manner different from that described on the summary of product characteristics (SPC) the minimum statutory withdrawal periods above will apply unless the medicine indicates a withdrawal period for the species concerned.

- There are specific requirements for labelling of products to be used under the Cascade and also for record keeping. Further detailed information is found in the body of the guidance note.

FURTHER INFORMATION

- For more information on the requirements of the prescribing Cascade please contact the VMD's Legislation team on 01932 338321 or alternatively contact VMD reception on 01932 336911 and quote "Cascade".

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Introduction

1. This is one of a series of Veterinary Medicines Guidance Notes (VMGNs) explaining the requirements of the Veterinary Medicines Regulations (VMR). The VMR are revoked and replaced on a regular basis, 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 VMGN. The VMGN will be updated as necessary and the date of the most recent update is shown on the front cover.

2. The VMR set out the UK controls on veterinary medicines, including their manufacture, advertising, marketing, supply and administration. VMGN 1 Controls of Veterinary Medicines provides basic information about the scope of the VMR, which can be found on: http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx Additional information, including the requirements for Marketing Authorisations (MAs), is given in VMGN 2 Marketing Authorisations for Veterinary Medicinal Products which can be found on: http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

The Authorisation Process and the Controls on the use of medicines in animals

3. Applications for authorisation of veterinary medicines are scientifically assessed against statutory criteria of quality, safety and efficacy. This assessment process evaluates the benefits of the product and takes account of potential risks to the environment, to animals, to people who administer the medicine and to those who may consume produce from treated animals. It also forms the basis of a benefit:risk evaluation on which the decision to grant an authorisation is based. A summary of product characteristics (SPC) is prepared at the end of the assessment process and lists information such as dosage, posology, indications, withdrawal period if relevant, and specific warnings for the safety of the species, users and environment.

4. The use of medicines in ways that have not been authorised may pose potential risks that the authorisation process seeks to minimise. The law therefore requires that, wherever possible, only medicines authorised for the condition and species being treated are used. The law also imposes controls on the administration of veterinary medicines and prohibits the administration of a veterinary medicine unless it is authorised and the administration is in accordance with its SPC. The VMR also prohibit the prescription, supply and administration of medicines unless these activities have been carried out by an appropriate person in accordance with controls on distribution. Non-compliance with the provisions is an offence and may result in prosecution.

5. However, the legislation recognises that there will be clinical situations where no suitable authorised veterinary medicine is available. The law provides exemptions to allow a veterinary surgeon to treat animals under his or her care in this situation. These exemptions are:

- **Products Administered for Research**
  Medicines administered in accordance with an animal test certificate (ATC) or a licence issued under the Animals (Scientific Procedures) Act 1986.

- **Exceptional Circumstances**
  In the event of serious epizootic diseases the VMD, acting on behalf of the Secretary of State, may permit in writing the marketing and use of immunological products without an MA.

- **Immunological Products for Imported/Exported Animals**
  Where an animal is being imported from, or exported to, a country that is not in the European Economic Area (EEA), the VMD may permit the use of an immunological product that is not authorised in the UK but is authorised in the exporting/importing country. The EEA comprises the European Union (EU) plus Iceland, Liechtenstein and Norway.

- **The Cascade**
  The cascade allows veterinary surgeons to legally prescribe medicines that are not authorised for the relevant clinical case or for the relevant species under treatment when there is no authorised veterinary medicinal product (VMP) available.

The Principles of the Cascade

6. The Cascade is a risk based decision-tree to help veterinary surgeons decide which product to use when there is no authorised veterinary medicine available. Without the Cascade, veterinary surgeons would only be allowed to prescribe veterinary medicines that are authorised for a given species and for a given condition.

7. The Cascade is based on the principle that, if there is no veterinary medicine authorised in the UK for treating a disease, the veterinary surgeon responsible for the animal may, in particular to avoid unacceptable suffering, treat the animal with a product from one of the following categories in descending order of suitability:

   a) A veterinary medicine authorised in the UK for the same condition in another animal species or for another condition in the same animal species;

   b) Either:

      (i) a medicine authorised in the UK for human use; or

      (ii) VMP not authorised in the UK but authorised in another Member State (MS) for use in any animal species in accordance with an import certificate issued by the VMD (for further information on the Import Certificate Scheme please refer to VMGN 5 Import Certificate Schemes, which is published on the VMD website:
      http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

   c) A medicine prescribed by the veterinary surgeon responsible for treating the animal and prepared extemporaneously by a veterinary surgeon, a

pharmacist or a person holding an appropriate manufacturer's authorisation (so called "specials manufacturer"). Under exceptional circumstances medicines may be imported from third countries in accordance with a VMD Import Certificate.

8. A medicine prescribed in accordance with the Cascade may be administered by the prescribing veterinary surgeon or by a person acting under the veterinary's surgeon's direction. The responsibility for the prescription and use of the medicine remains with the prescribing veterinary surgeon.

Considerations on the legal use of Cascade

9. The Veterinary Medicinal Products Directive 2001/82/EC (as amended) sets out the controls on the manufacture, authorisation, marketing, distribution and post-authorisation surveillance of veterinary medicines applicable in all MS. The Directive provides the basis for the UK controls on veterinary medicines, which are set out nationally in the VMR.

10. The European Commission (EC) has acknowledged that insufficient authorised VMPs are available for the treatment of every clinical case in every species. Therefore, Directive 2001/82/EC allows, under Articles 10 and 11, veterinary surgeons to prescribe products that are not authorised for the relevant clinical case or for the relevant species - this provision is known as the Cascade. This is a derogation from the main requirement in the EU legislation to use authorised veterinary medicines - therefore the Cascade increases the range of medicines that a veterinary surgeon can use.

11. In the UK the Veterinary Medicines Directorate (VMD) has fully implemented the Cascade into national legislation under Schedule 4(1) of the VMR.

12. As already mentioned elsewhere in the VMGN, every indication and dosage recommendation authorised for a VMP is derived from scientific data produced by the manufacturing authorisation holder (MAH) and has been subjected to a benefit:risk assessment. This information is set out in the SPC. For example, where the SPC specifies a particular dosage regimen or vaccination schedule in a named target species and for a named indication, there has been data assessed by the VMD to show that the product can be used safely and efficaciously in these circumstances.

13. The decision tree in the Cascade seeks to allow veterinary surgeons to use their clinical judgement to treat an animal under their care. However, when a product is used under the Cascade, it means that no data or insufficient data have been submitted to the VMD to support the authorisation of this differing dosage regimen or indication.

14. In departing from the clinical particulars on the SPC the veterinary surgeon must balance the benefits against the risks of doing so and thus take responsibility for their clinical decision. The potential benefits of using the product are usually obvious but the risks may not be. Risk could relate to the animal, the owner or person administering the product, consumers (where veterinary medicine residues in food might be affected), the environment and even wider public health (for example where increased selection for antimicrobial resistance might be the outcome). Any departure from the SPC must be considered carefully as the advice and warnings

given are there for good reason and based on assessed data. To ignore or disregard them without due care and thought would be inappropriate and, if something goes wrong with the treatment, could lay the veterinary surgeon open to litigation.

15. The aims of the existing legal provisions are to ensure that unauthorised medicines are used only when there is no authorised product for the condition and species concerned. In the case of food-producing animals, the aims are to ensure that potentially harmful residues of veterinary medicines do not enter the food chain. Definitive interpretation of legislation can only be given by the Courts. It is likely that the legislation will be interpreted in the light of how a competent and professional veterinary surgeon would reasonably act in pursuance of the aims in a particular set of circumstances. Please see Annex A for some illustrative, practical examples of the VMD's view of how the Cascade provisions may be applied.

The term "off-label use"

16. The term "off-label use" is regularly used but there are different interpretations as to what it means. There is no definitive legal definition for the term - for this reason this VMGN avoids the use of this misleading terminology and refers only to "authorised use" and "Cascade use".

17. Authorised use corresponds to the situation where a product is used in accordance with the clinical advice given on the SPC, for example the indications, dosage regime, contra-indications, target species safety warnings.

18. Cascade use corresponds to the situation where a product is used in a different species or when it is used in the authorised target species but for a different condition (which may or may not require a different dose) to that specified on the SPC. Where a product is used in accordance with the clinical particulars given on the SPC, but certain warnings/advice are not taken into account this is not considered to constitute Cascade use and may represent a safety risk (eg,failing to follow the user warnings on protective clothing such as gloves). In some cases, it may constitute illegal use (e.g., supplying a product outside its expiry date).

19. Please see the Annex A to this VMGN for some practical examples of authorised and Cascade use of veterinary medicines.

Prescribing under the Cascade

Food producing animals

20. If there is no medicine authorised in the UK for a condition affecting a food-producing species, the veterinary surgeon responsible for treating the animal(s) may use the Cascade options as set in paragraph 7 except that the following additional conditions apply:

- the treatment in any particular case is restricted to animals on a single holding;
- any medicine imported from another MS (option b(ii)) must be authorised for use in a food-producing species in the other MS;

- the pharmacologically active substances contained in the medicine must be listed in the Table of Allowed Substances in Commission Regulation EU No 37/2010 – Maximum Residue Limits (MRLs) available at http://ec.europa.eu/health/files/eudralex/vol-5/reg_2010_37/reg_2010_37_en.pdf

- the veterinary surgeon responsible for prescribing the medicine must specify an appropriate withdrawal period;
- the veterinary surgeon responsible for prescribing the medicine must keep specified records.

21. This provision does not specifically require an MRL to be set for the species for which the veterinary surgeon intends to use it. Therefore, even if the MRL entry for that substance does not include e.g. eggs, a veterinary surgeon could consider it for use in chickens intended to produce eggs for human consumption. In this case the veterinary surgeon should consider the risks of using this substance and is obligated to consider the time of use in relation to the stage of development of the eggs and the length of time between administration of the last dose and the first egg being laid and to set an appropriate withdrawal period to ensure that residues of any substances administered will not enter the food chain.

22. These additional provisions are to safeguard consumers of produce from treated animals against risk from any potentially harmful residues of the medicines administered.

Setting an appropriate withdrawal period for food producing species treated with medicines under the Cascade

23. The withdrawal period is the period of time following treatment of animals with a veterinary medicine in which the meat, milk, eggs or honey from the treated animal must not enter the human food chain due to the possible presence of residues from pharmacologically active substances. It is determined by scientific studies conducted on the target species and is stated on the SPC for the authorised medicine.

24. Where a product is used under the Cascade in a food producing species the veterinary surgeon is responsible for defining an appropriate withdrawal period in all cases. Such a withdrawal period has to be selected to ensure that residues above the MRL will not occur. If the product is administered to a species not identified on the SPC, or to an authorised species but at a higher dosage than recommended, it is necessary to apply the **minimum** statutory withdrawal periods, or the withdrawal period stated on the SPC, whichever is longer. The minimum statutory withdrawal periods are as follows:

    - 7 days for eggs and milk
    - 28 days for meat from poultry and mammals
    - 500 degree days for meat from fish

25. For products imported under a Special Import Certificate (SIC), provided that the product is used strictly according to the terms of its EU authorisation, the withdrawal period applied in the UK should be the period stated on the EU product literature. For products imported under an SIC and used in a way different from that described

on the SPC then the UK minimum statutory withdrawal periods will apply or the withdrawal period stated on the SPC, whichever is longer.

26. As there is no minimum withdrawal period set for honey, it is up to the prescribing veterinary surgeon to set a suitable withdrawal period that will ensure no risk to consumer health. Further guidance on setting a suitable withdrawal period is available from the National Bee Unit (telephone: +44 (0) 1904 465636).

27. Human homeopathic products may be used in food producing animals under the rules of the Cascade, but only if the pharmacologically active substances are listed in Table 1 Allowed Substances of Commission Regulation No 37/2010. In this case, the statutory withdrawal period must be applied.

The use of the Cascade in horses

28. As first choice, horses should be treated with VMPs which have a UK MA for use in horses. However, if there is no suitable authorised product available, the Cascade may be used to prescribe an alternative medicinal product.

29. A horse declared as non-food producing in its passport can be treated under the Cascade as a companion animal. A horse that has not been signed out of the food chain in its passport can only be treated with a veterinary medicine that contains pharmacologically active substance(s) listed in Table 1 of Regulation EU 37/2010 for use in a food producing species. Products imported from another MS, or in exceptional circumstances from Third countries, in accordance with a VMD Import Certificate may also be used, providing that a withdrawal period can be set.

30. Commission Regulation 122/2013 amending Commission Regulation 1950/2006 establishing, in accordance with Directive 2001/82, a list of substances essential for the treatment of equidae, which can be found on:
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2013:042:0001:0017:EN:PDF.
This legislation allows the use of certain substances in horses (declared as food or non-food producing in the passport) under the use of the Cascade and with a statutory withdrawal period of six months.

31. Detailed information on the use of medicines in horses in the context of the horse passport legislation may be found in VMGN 16 Guidance on Horse Medicines and Horse Passports, which is published on the VMD website
http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Use of human medicines

32. The veterinary medicine sector is a much smaller market than the human medicine sector and it is also more complicated because of the different controls for food producing animal medicines and companion animal medicines. There is a general assumption that human and veterinary medicinal products containing the same active substances are interchangeable. This is not always the case and the human medicine has no specific safety or efficacy data on its use in animals to corroborate this.

33. For example, animal species react differently to medicines between themselves (e.g. permethrin works in dogs but is poisonous to cats) and humans (e.g. ibuprofen is

poisonous to dogs) so controls are required on inter species use except where this has been authorised. These risks relate to all the components of the medicine, not just the active ingredient. There exists the risk that other constituents in the formulation of the human medicine will affect the safety and efficacy of the medicine when used in animals

34. Medicine selection under the Cascade is totally under the responsibility of the prescribing veterinary surgeon. The VMD does not seek to interfere with the veterinary surgeon's clinical judgment in determining the best available treatment to the animal under his or her care. The use of a human medicine under the Cascade is legal provided that the veterinary surgeon follows the Cascade decision tree and is able to justify the choice of treatment based on animal welfare. It is not permissible to use a human medicine simply because it is cheaper than an authorised veterinary medicine.

Prescription of extemporaneous preparations, including Specials

35. Neither European nor national legislation offers a definition of extemporaneous preparations. Our interpretation of the legal text is that any medicine tailored for a particular animal or herd, prepared by a veterinary surgeon, a pharmacist or a person who holds an appropriate manufacturing authorisation, is an extemporaneous preparation and may be used under the Cascade. A veterinary prescription is required but this prescription may be written or simply oral.

36. When it is necessary to have a medicine prepared as an extemporaneous preparation, in the first instance it is recommended that the veterinary surgeon contacts a manufacturer holding an authorisation that permits them to manufacture such products - a Specials Manufacturing Authorisation (ManSA). This is because premises that hold a ManSA are inspected for compliance with the principles of Good Manufacturing Practice (GMP) and therefore are well prepared and equipped to prepare a medicine of suitable quality.

37. Manufacturers of Specials are authorised by the VMD or, if they also manufacture human medicines, by the Medicines and Healthcare Products Regulatory Agency (MHRA).

38. A list of veterinary-only Specials Manufacturers can be found on the VMD website http://www.vmd.defra.gov.uk/pdf/register_specials.pdf — and a register of combined human and veterinary Specials Manufacturers can be found on the MHRA website: http://www.mhra.gov.uk/Howweregulate/Medicines/Licensingofmedicines/Manufacturersandwholesaledealerslicences/index.htm

39. For further information on the manufacture of Specials please refer to VMGN 15 Guidance for Manufacturers, which is published on the VMD website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

40. Medicines marketed under Schedule 6 of the VMR – Exemptions for small pet animals are available over the counter medicine and may be administered at any time in accordance with the product's recommended use. However, if the product is to be administered to an animal in a way not in accordance with the product literature (for example, the product is for ferrets and the veterinary surgeon wishes to use it in

a cat) because in his/her professional judgement, such a product could provide a safer or better option than an authorised medicine, then this would consist of use of a product under the Cascade (use of an extemporaneous preparation).

41. For further information please refer to VMGN 12 Exemptions for Small Pet Animals, which is published on the VMD website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

"Office stock" of medicines for use

42. In the interest of animal welfare, a veterinary surgeon may have in his possession medicinal products such as human medicines, imported medicines and extemporaneous preparations intended for administration to animals under the Cascade. The VMD does not specify a maximum quantity that may be held in a practice as this varies from practice to practice and will depend on the products involved. However, the quantity held should be justified by the clinical need under the Cascade rules – these medicines must not be used as a first choice treatment in every situation. It is important for veterinary surgeons to keep up to date with new authorisations and adjust their prescribing habits and stocking policies accordingly.

Dispensing of medicines

43. Only veterinary surgeons registered with the Royal College of Veterinary Surgeons (RCVS) may prescribe medicines under the Cascade for use in animals in the UK.

44. A Suitably Qualified Person (SQP) may dispense an authorised VMP, which falls within the scope of the qualification they hold, for use under the Cascade against a valid prescription from a veterinary surgeon.

45. A pharmacist may dispense authorised VMPs, human medicines or extemporaneous preparations against a prescription from a veterinary surgeon.

Labelling of medicines

46. The following information must be included on labels for products administered under the Cascade. Where the product is supplied in its original packaging and already includes some of this information which remains legible following application of the dispensing label, it is not necessary to repeat this information on the dispensing label. If it is not feasible to include all of the information on the label due to the size of the packaging it must be included on a separate sheet.

- the name and address of the pharmacy, veterinary surgery or approved premises supplying the VMP
- the name of the veterinary surgeon who has prescribed the product
- the name and address of the animal owner
- the identification (including the species) of the animal or group of animals
- the date of supply
- the expiry date of the product, if applicable
- the name or description of the product, which should include at least the name and quantity of active ingredient
- dosage and administration instruction

- any special storage precaution
- any necessary warnings for the user, target species, administration or disposal of the product
- the withdrawal period, if relevant, and
- the words “Keep out of reach of children” and “For animal treatment only

47. The veterinary surgeon prescribing under the Cascade must use his/her judgment to list the safety warnings that should be placed on the label of the dispensed medicine.

48. Unless the veterinary surgeon who prescribed the medicine both supplies the product and administers it to the animal in person, the person supplying the medicine must label it or give instruction for it to be labelled as described above.

Record keeping requirements

49. In addition to the standard record keeping requirements set out in VMGN 14 Record-Keeping Requirements for Veterinary Medicinal Products, which can be found on the VMD website http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx there are specific record keeping requirements for veterinary surgeons who administer or supply medicines to be used under the Cascade. These are set out below and must be retained for at least 5 years and be made available on request to a duly authorised person.

50. The information recorded must include the following:

- date of examination
- owner’s name and address
- the identification and number of animals treated
- result of the veterinary surgeons clinical assessment
- trade name of the product(s) prescribed, if applicable
- manufacturer’s batch number
- name and quantity of the active substance
- doses administered
- duration of treatment
- withdrawal period

51. If the client or other records already have this information no additional separate records are needed as long as the information is accessible on request. Veterinary surgeons may also find it helpful to include information identifying treated animals among their records.

Informed consent before treatment of animals

52. It is not a legal requirement under the VMR to obtain informed consent from the owner of an animal to be treated under the Cascade. This requirement is part of the RCVS Code of Professional Conduct for Veterinary Surgeons which can be found on:

http://www.rcvs.org.uk/advice-and-guidance/code-of-professional-conduct-for-veterinary-surgeons/
The VMD supports this initiative in the interest of good communication between client and practitioner.

Reporting of an adverse event

53. It is not a legal requirement for veterinary surgeons to report adverse events (AEs) to medicines prescribed under the Cascade. However, we encourage reporting of any AEs to the MAH or to the VMD as this will provide us with knowledge of the use of the medicine in the field. Unless such reports are received the incidence and severity of side effects, and the ongoing efficacy of products, cannot be assessed, and consequential action, for example, to amend product literature, cannot be taken. Further information on the VMD's AEs scheme may be found in VMGN 11 Pharmacovigilance Guidance on Adverse Events, which is published on the VMD website: http://www.vmd.defra.gov.uk/public/vmr_vmgn.aspx

Further Information

54. Further information is available from the Veterinary Medicines Directorate, Woodham Lane, New Haw, Addlestone, Surrey, KT15 3LS - Tel: +44 (0)1932 336911; Fax: +44 (0)1932 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.defra.gov.uk).

ANNEX A

PRACTICAL CONSIDERATIONS CONCERNING THE USE OF THE CASCADE

A) When is treatment considered "authorised use" or "Cascade use"?

When a veterinary medicine is used in another species or to treat another disease this is clearly Cascade use. However, there may be some situations where it is not so immediately apparent that use is under the Cascade provisions.

The following table is intended to provide some examples of areas where guidance may be helpful in clarifying the position. It is not intended to be a comprehensive list but offers examples based on previous queries posed by veterinary surgeons. Decisions on whether a product is being used under the Cascade are integrally linked to the very specific wording on that product's SPC. **It is essential to emphasise that specific decisions on whether use is Cascade use can only be reached when all relevant SPC sections are taken into account.**

Scenario	Cascade use (not supported directly by VMD assessed data)	Authorised use (supported by VMD assessed data)
The SPC dose regimen is 10 mg/kg for 3 days and the applied dose regimen is 20 mg/kg for 3 days.	✓	
The SPC dose regimen is 10mg/kg but this is extended in duration from a recommended 3 days to 6 days.	✓ (from days 4 to 6)	✓ (from days 1 to 3)
The SPC dose is 10 mg/kg for 6 days and the applied dose regimen is 20 mg/kg for 3 days.	✓	
The SPC includes special warnings concerning the use of the product in animals with kidney disease but the animal to be treated has kidney disease.		✓ (as long as special warnings followed)
Anticancer drug indicated for use in dogs with tumours with specific genetic markers – used in dogs with tumours not displaying the markers or the tumour markers are not established	✓	
The SPC for the vaccine specifies primary vaccination in animals from 10 weeks of age or older, and animals are 12 weeks at the time of vaccination.		✓
The SPC for the vaccine recommends a primary schedule of vaccination at 6 and 12 weeks but the animal to be treated is vaccinated at 8 and 14 weeks.		✓

B) Special consideration for use of vaccines under the Cascade

Where the SPC for a vaccine specifies a booster vaccination for a component after three years but an annual booster vaccination is carried out this is Cascade use.

Where an animal is to be revaccinated beyond the period of the authorised schedule (e.g. an adult dog being revaccinated some time after puppy vaccinations) there is no requirement that you must use the same product on the animal as was used previously. Veterinary surgeons should make a risk:benefit assessment taking into account current knowledge concerning the individual disease against which they are vaccinating. For example, there may be no real justification for administering a full primary puppy vaccination course for the WSAVA (World Small Animal Veterinary Association) recommended core antigens (i.e. Distemper, Adenovirus and Parvovirus) when a dog's booster vaccination schedule has been allowed to lapse, as a single dose of vaccine may be sufficient to provide adequate immunity. This is not the case for antigens, such as, leptospira and so it is important for veterinary surgeons to make a benefit:risk assessment in relation to the specific animal and its circumstances.

Simultaneous and concurrent use of vaccines
Where SPCs specifically state that two named vaccines can be administered:

- concurrently
  - at the same time at different sites or
  - at the same site at different times or
- simultaneously (i.e. they can be mixed together immediately prior to administration)

There will be data to show they are compatible and that there are no adverse effects on the safety and efficacy of either individual product. Where there is no such SPC statement, no data have been assessed by the VMD to demonstrate whether the two products could interact in such a way as to adversely affect the immune response to either product and/or have the potential to cause significant adverse reactions. Therefore, in this case, concurrent or simultaneous administration represents Cascade use. A decision to use a vaccine before or after any other VMP needs to be made on a case by case basis by the veterinary surgeon.

Use of a route of administration other than the authorised route
Safety and efficacy data have been generated using the route of administration stated on the SPC. This is of particular relevance to live vaccines where safety, in respect of reversion to virulence and the likelihood of dissemination and spread of the live virus, has been established. This demonstrates that using the authorised route of administration is safe. Use of an unauthorised route of administration could have serious consequences for the animal, the owner, the environment and the consumer if the attenuated virus behaves differently when administered by a different route (e.g. administering a vaccine intended for intramuscular administration in drinking water or feed).

C) Some illustrative examples of the VMD's view of how the Cascade provisions may be applied, in particular regarding companion animals

- **Dosage Considerations** - Sometimes a veterinary surgeon may consider that the effective treatment of a particular condition in a particular animal requires a different dosage regime from that on the label of a product. In such circumstances recourse to the Cascade would be appropriate and the veterinary surgeon may compare the merits of using that product with a dosage regime different from that described on the product's SPC with an alternative authorised veterinary medicine. If neither can

safely be administered at the dosage required, the veterinary surgeon should consider further options under the Cascade.

- **Individual Characteristics** - If a particular animal has characteristics, such as age, general condition or known sensitivity to a particular substance, which the veterinary surgeon judged to present unacceptable risks and to contra-indicate the use of the authorised product, he or she could conclude that no authorised product existed for that condition in that animal and consider other treatments.

- **Chronic Infections** - If a condition persists following treatment with an authorised product, the veterinary surgeon may consider in a particular case that there is no authorised treatment for that particular condition and that further use of medicines containing substances in the same chemical group is not appropriate. In such circumstances it would be legitimate to consider alternatives in accordance with the Cascade.

- **Complex Conditions** - Diagnosis is a matter for the veterinary surgeon under whose care an animal or animals have been placed. Some conditions need to be viewed more widely and treated accordingly. For instance, pneumonia may be regarded as a single condition. On the other hand, the diagnosis may be of more than one concurrent condition, such as pneumonia with fluid retention. In such circumstances the veterinary surgeon would need to exercise his or her professional skills to reach a diagnosis and prescribe the most effective treatment.

  If he or she considered that in the circumstances there were two or more concurrent conditions, the treatment of each would need to be considered in accordance with the VMR. However, due account of the usual factors such as drug incompatibilities or side-effects must be considered.

- **Unavailability of Products** - If a product cannot be obtained despite diligent search and in a reasonable time, the veterinary surgeon may conclude that in the circumstances it does not exist. In such circumstances the Cascade should be followed to identify a suitable alternative. However, it is appreciated that there may be cases where urgency dictates that a veterinary surgeon uses whatever is to hand, whether authorised or not. The VMD publishes on its website details of supply issues which have the potential to cause animal welfare issues and provides where possible information on alternative products. http://www.vmd.defra.gov.uk/vet/supply.aspx

- **Animal owner considerations** - If a veterinary surgeon considers that, for example, an elderly or disabled pet owner would have difficulty in crushing and administering tablets which were the only form in which an authorised product was available, it would be unlikely that action would be taken if he or she concluded that medicine in tablet form were not appropriate in the circumstances, and alternatives in line with the Cascade were considered.

- **Medicines commonly found around the home** - Sometimes a veterinary surgeon may judge there is a need to alleviate a pet's discomfort until a home visit can be made or the animal brought to the surgery. It would be unlikely that action would be taken if in such circumstances a home remedy, e.g. antihistamine, were to be recommended. This means that in an emergency a vet could recommend that an animal owner could use a human medicine that the owner already has in his/her

possession. This does not mean a pet owner should be encouraged to go into a pharmacy and ask for a human medicine for their pet.

List of Abbreviations

AE	Adverse Event
ATC	Animal Test Certificate
Defra	Department for Environment, Food & Rural Affairs
EC	European Commission
EEA	European Economic Area
EU	European Union
GMP	Good Manufacturing Practice
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
ManSA	Specials Manufacturing Authorisation
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Member State
RCVS	Royal College of Veterinary Surgeons
SIC	Special Import Certificate
SQP	Suitably Qualified Person
SPC	Summary of Product Characteristics
VMD	Veterinary Medicines Directorate
VMGN	Veterinary Medicines Guidance Note
VMP	Veterinary Medicinal Product
VMR	Veterinary Medicines Regulations

VETERINARY MEDICINES GUIDANCE NOTE

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