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The 'cascade' and human generic products

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ABSTRACT: The 'cascade' is often referred to in veterinary medicine. In this article, Donal Murphy of the National Office of Animal Health, the UK trade association for the veterinary medicines sector, explains what it is, how it helps ensure that animals can be treated with a range of products, how it actually increases the range of medicines that can be used and why adherence to the requirements of the 'cascade' is important.

What is it?

The 'cascade' is a concept describing long-standing legal flexibility which provides a rational balance between the legislative requirement for veterinary surgeons to prescribe and use authorised veterinary medicines – where they are available – and the need for professional freedom to prescribe other products where they are not. It is intended to increase the range of medicines available for veterinary use.

When a veterinary medicine is authorised for use by one of the independent regulatory authorities – in the UK, the Veterinary Medicines Directorate (VMD) – the product is given a Marketing Authorisation (MA), which is the licence that allows the company to market and sell the product.

The part of the Marketing Authorisation which details how the product can be used is known as the Summary of Product Characteristics, or SPC. For example, the SPC gives:

- the name, strength and pharmaceutical form of the product
- the name and strength of each active substance
- the animal species to which it can be administered
- what diseases it can be used to treat or, in the case of vaccines, what diseases it prevents
- the shelf life.

It also gives safety warnings, which may include:

- warnings about the product's use, for both the person administering the product and for the animal(s) to which the product is being administered
- information about the safe disposal of the product and its packaging, to ensure user safety and to protect the environment.

In the case of food-producing animals, the SPC also gives withdrawal periods – how long after the product has been administered can the meat, milk or eggs from that animal be consumed.

What is the difference between 'off-label' and 'cascade' use?

The term 'off-label' use is regularly applied in discussions about the 'cascade', but there are different interpretations as to what it means. Indeed, there is no definitive legal definition for the term 'off-label' use.

For this reason, the Veterinary Medicines Directorate (VMD), in its Veterinary

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Medicines Regulations Guidance Note (VMRGN) avoids the use of this misleading terminology and refers only to 'authorised use' and 'cascade use'. Thus, any use outside the authorised indications stated in the SPC is 'cascade use'.

Who can prescribe products under the 'cascade'?

Only veterinary surgeons are permitted to prescribe products for use in a manner other than that which is authorised – that is, 'cascade use'. Other prescribers of licensed veterinary medicines, such as Suitably Qualified Persons (SQPs) or pharmacists, are not permitted to prescribe products for use outside the terms of the Summary of Product Characteristics.

What do vets need to do to comply with the 'cascade'?

If there is no medicine authorised in the UK for a specific condition, the veterinary surgeon responsible for treating the animal(s) may – in order to mitigate unacceptable suffering – treat the animal(s) with a product in accordance with the following sequence or 'cascade':

a. a veterinary medicine authorised in the UK for use in another animal species or for a different condition in the same species; or, if there is no such product;
b. either:
   i. a medicine authorised in the UK for human use, or
   ii. in accordance with an import certificate from the VMD, a veterinary medicine from another Member State; or, if there is no such product;
c. a medicine prepared extemporaneously, by a vet, pharmacist or a person holding an appropriate manufacturer's authorisation.

If the animal(s) are food-producing animals, then the following additional conditions apply:

- the treatment in any particular case is restricted to animals on a single holding
- any medicine imported from another Member State must be authorised for use in a food-producing species in the other Member State
- the pharmacologically active substances contained in the medicine must have a Maximum Residue Limit, or MRL
- the prescribing vet must specify an appropriate withdrawal period – there are statutory minimum withdrawal periods for medicines prescribed to food animals under the 'cascade' in the Veterinary Medicines Regulations
- the prescribing vet must keep specified records.

A medicine prescribed in accordance with the 'cascade' may be administered by the prescribing vet or by a person acting under their direction – a veterinary nurse or animal owner, for example. Responsibility for the prescription and use of the medicine remains with the prescribing veterinary surgeon.

> "The 'cascade' is a long-standing legal flexibility which provides a rational balance between the legislative requirement for veterinary surgeons to prescribe and use authorised veterinary medicines – where they are available – and the need for professional freedom to prescribe other products where they are not."

Why is it important to use authorised medicines when there is a suitable licensed veterinary medicine?

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.

Animal species react differently to the same medicines. For example, permethrin works in dogs but is poisonous to cats, and 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 or excipients in the formulation of the human medicine will affect the safety and efficacy of the medicine when used in animals.

Animal species also have many physiological differences from humans and from each other. As a result they may react differently to medicines.

The authorisation system for veterinary medicines requires a product to have proven quality and effectiveness and, most importantly, safety for the animal, the user (vet, farmer, pet owner), the environment and, for food animals, the consumer of the animal or its by-products. This assurance has to be provided for each species and each indication on the label.

In addition, animal medicines containing the same active ingredient as human medicines may be formulated differently. For instance, the formulation criteria to ensure that a drug is properly absorbed through the gut of a human will differ from those for a cat, because the feline gut is rather shorter than that in a human. Human medicine formulations may contain different excipients or have different bioavailability from veterinary medicines. Using a product which is not authorised for animals, therefore, increases the risk of harm to the patient.

In addition, the cost of developing a medicine for animal use is high and can involve much research and many tests not carried out for human medicines. The use of human medicines, in place of the equivalent authorised veterinary medicine, can only be done by referring to the information on medicine use provided by the animal medicine companies.

Assuming the data are transferable is potentially hazardous and doing so takes advantage of work done by the animal medicine industry, without paying for it. This means that those users abiding by the rules are subsidising those who do not; and such abuse diverts essential funding away from future research and development on new veterinary medicines.

What is a generic product?

It is important to address the potential confusion with the use of the word 'generic'.

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Authorised veterinary generics exist legitimately and can be used by vets similarly to other authorised animal medicines. These products are effectively a 'copy' of the original, pioneer copy and were authorised for development after the data protection period for the original product had expired.

However, human generic medicines – that are similar to the authorised veterinary medicines – also exist, but may not be used in preference to a licensed veterinary medicine, unless there is no suitable veterinary medicine available.

As previously stated, the 'cascade' provides a legal mechanism allowing veterinary surgeons to use their clinical judgement to prescribe a suitable medicine where no authorised medicine exists. Use and prescription by vets of human generic medicines where a suitable veterinary product is available is a criminal offence and contrary to the RCVS *Guide to Professional Conduct*.

Vets remain entirely responsible for the treatment of animals under their care. The use of a medicine under the cascade must be capable of being supported by clear, auditable clinical evidence to justify the vet's decision.

Why is it important to respect and adhere to the 'cascade'?

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. To put this into perspective, the total UK market for all animal medicines is worth approximately £500 million, whereas the human pharmaceutical market is estimated at £13 billion. This huge difference is exemplified by the fact that the global sales of one single human medicine, Lipitor, are greater than the whole of the global animal health market.

For large animal medicines there are, of course, additional studies required to secure an MRL and withhold times.

Current benchmarking studies show that the animal health industry spends €40-60 million on getting a new companion animal medicine to market, and €80-100 million for a medicine for use in a food-producing species.

The time to market is between eight and 12 years. The data protection period for a new product is only eight plus two years. In other words, after eight years of a drug's being on the market, an application can be made to introduce a generic equivalent to be put on the market only two years later – after the 10th year on the market for the pioneer product.

Therefore, in the animal health sector, the period for a return on investment for research and development costs is very short. If human medicines are used in place of authorised veterinary products – simply for short-term financial gain at a practice level – it means there may be even fewer new products for the animal health market in the future, because there is less incentive for pharmaceutical companies to invest in the sector.

Summary of the animal health industry perspective

- Human medicines should be used only when no licensed veterinary equivalent is available – cytotoxics, for example.
- Human medicine formulations may contain different excipients or express different bioavailability characteristics; and, therefore, may not provide the same therapeutic effect as the correct veterinary authorised medicine.
- Human generics make no contribution to the cost of veterinary research and new molecules for medicines for the treatment of Minor Use Minor Species (MUMS) – such as bee medicines and goat medicines.
- The use of human medicines, especially when authorised veterinary products exist, threatens the future development and availability of new products for companion animals.
- It also places a burden on the expertise of the individual vet – extrapolating from one species to another, when the SPC is not available for use in animals.

Conclusion

Animals need medicines to help prevent disease and to help treat them if they do fall ill. All species deserve the benefit of medicinal products which have been specifically developed and authorised for their treatment.

The 'cascade' ensures that this happens, wherever possible; but also gives flexibility for veterinary surgeons to use their clinical judgement to prescribe a medicine where no veterinary authorised medicine exists.

For further information, see the VMD's Veterinary Medicines Guidance Note 13, Guidance on the use of the cascade, available at: www.vmd.defra.gov.uk/pdf/vmgn/VMGNote13.pdf vnj

NEWS REVIEW
by Jean Turner

Manchester nurse wins bursary

A veterinary nurse from Manchester's PetMedics has won the 2012 Royal Canin bursary, run in conjunction with the BVNA.

Lisa Coulborn RVN won the £500 prize, beating off competition from more than two dozen other VNs, to enable her to begin the VPMA's Veterinary Practice Administration Certificate.

Lisa explained: 'After having worked as a veterinary nurse for the past 15 years, I have recently developed a passion for good management, which is only growing stronger as I see how important it is to practice staff and clients. I'm currently on maternity leave and keen to make a start on the VPMA course and so Royal Canin's generous bursary will help me to realise this goal. Needless to say, I'm delighted!'

Royal Canin's veterinary marketing manager, Lindsay Calcraft, explained: 'Each year, we partner the BVNA to offer an annual bursary aimed at helping nurses to further their education. We wish Lisa well in her impending studies and can confirm that we will be continuing the bursary scheme in 2013. Next year's bursary will be calling for entries with a specific focus on nutrition.'

For more information, visit www.royalcanin.co.uk or contact your Veterinary Business Manager. vnj

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