

The Cascade

Important Information Regarding the 'Cascade' of use which applies in the UK when using medicines to treat animals.

Abridged Article dated January 2008

This Article is aimed at the veterinary profession but may be of interest to all users of animal medicines.

Background

The cascade has been largely unchanged since 1995. The concept provides a veterinary surgeon (and only a veterinary surgeon) with an important derogation from the general restrictions on the use of veterinary medicines.

Outside of a veterinary surgeon's prescription, the use of medicines must be strictly in accordance with the conditions of the marketing authorisation and the label directions should be closely followed.

When the European legislation was drafted it was recognised that the veterinary market for medicines is small in comparison to that for human medicines and therefore it is likely that there would be many diseases where veterinary medicines would be unavailable. Thus, when there is no suitable medicine available, the cascade permits veterinary use of medicines intended for other clinical indications or species, specifically under the direction of a veterinary surgeon, thus recognising that the veterinarian is best placed to take the risk management decision associated with the use of an unauthorised medicine.

The Issue

Prior to the revision of the European Directive and the subsequent production of the Veterinary Medicines Regulations 2005, use of the cascade by veterinary surgeons had become considerably lax, to the extent that human authorised products were being used routinely despite the availability of suitable authorised veterinary products. Where the only consideration being applied is the cost of the medication and particularly where no clinical judgement is being applied, the cascade derogation does not and has never permitted this.

At that time veterinary surgeries were openly stocking and prescribing human generic products as a routine when the law stated clearly that the use of the cascade provisions should be exceptional and the decision to use the cascade should be taken for each individual patient for the primary reason of avoiding unacceptable suffering.

The production of the new Veterinary Medicine Regulations provided the opportunity for the guidance associated with the legislation to be revised and this was done to clearly exclude the routine use of human generic products where a suitable veterinary medicine is authorised.

Previous Guidance

Previous VMD guidance had suggested the use of human generics might be acceptable in the exceptional circumstance where the health and welfare of an animal could be compromised because the owner lacked funds. However, the way this was being implemented by the profession had become a significant problem and certainly not within the spirit of the legislation or guidance. In fact the guidance statement was being generally interpreted as a loophole allowing the use of human generics routinely and these products were being promoted and encouraged by being freely available through the veterinary distribution and supply chain.

As a result the guidance note, not the legislation, has been redrafted to address this problem and the VMD has, as part of its responsibilities, made sure this change has been highlighted and has sought to make clear the consequences of failing to observe the law on veterinary medicine use.

Accountability

It is worth stressing the prescribing veterinary surgeon's duty to ensure they understand the risks of resorting to the cascade in all its forms; their duty to ensure their client is made aware of the risks; and the need to take due precaution to reduce those risks as far as possible. The advice from the VMD setting out the likelihood of prosecution where a veterinary surgeon does not follow the cascade rules is not intended to be a threat but an attempt to make veterinary surgeons aware that, should they be challenged about a prescribed medication, their defence could be heard in a court of law. For it is the courts that will ultimately interpret the legislation and the most likely route to the courts will arise through a challenge from an aggrieved client. At all times therefore, a veterinary surgeon should be prepared to defend their prescription by demonstrating compliance with the law and acceptability of their clinical choice through support from peer or expert opinion. Such defence may not be readily available where a human generic product has been used instead of the authorised veterinary medicinal product.

The VMD does have a role to ensure that the legislation is enforced. We prefer to do this through advice and education in the first instance. The use of human generic medicines where suitable authorised veterinary medicines are available is not consistent with the cascade provisions and clearly contravenes the law.

Enforcement/Seizure

Where illegal products are discovered it is now common practice for our inspectors to seize and destroy them without compensation. A Seizure Notice will also be issued and published. Where repeated contravention occurs this may lead to prosecution depending on the seriousness of the offence. However, in its enforcement of the legislation, the VMD will not generally seek to question the clinical judgement of the veterinary surgeon.

Rationale for use of authorised veterinary medicines

The underlying tenet supporting the use of human generics by a small number of veterinary practices appears to be the assumption that they are equivalent to an authorised veterinary medicine. This assumption can be flawed for a number of reasons. In authorising a veterinary generic product the application will be supported by data derived from bioequivalence studies comparing the performance of the generic product to an authorised pioneer product in the target species. Human generic products lack this data comparison with the authorised veterinary product they would displace and as far as VMD is aware such data will not exist. Proof of bioequivalence is an essential step in the authorisation process for generics. If two products are proven to be bioequivalent this provides evidence to demonstrate that *in-vivo* they behave sufficiently similarly to be confident that the two products will be equally efficacious.

There are many examples of where the VMD has authorised veterinary generic products and all of them are supported by suitable data as a basis for this scientific proof. Authorisation however, cannot be achieved using, a visual comparison of labels, anecdotal information, assumption of equivalence or a history of apparently satisfactory past use.

There are other reasons why the use of an authorised veterinary product is preferable which veterinary surgeons should consider.

1. Medicines not authorised for veterinary use represent an undefined risk to the patient, owner, consumer and environment.
2. Should an adverse reaction occur any approach to a human generic company is unlikely to generate an adverse reaction report to the VMD.
3. Product recalls for a human generic product may omit the veterinary user as this is not a recognised sales route.
4. Contacts with the pharmaceutical company marketing human medicines (this is the address on the label) are likely to be met with a lack of knowledge on veterinary use.
5. Contact with and support from the pioneer company for advice is inappropriate.
6. There is no underlying assurance provided for animal use of a human generic by a supporting regulatory process.

In short safety and efficacy of the human generic medicine in animals is an assumption, not a fact backed by science, and decision making in modern veterinary practice is intended to be science based.

The reporting of veterinary adverse reactions following human medicine use is unreliable for a variety of obvious reasons. For example, the small number of adverse reaction reports in animals to human medicines is likely to be due to failure to report rather than lack of adverse reactions, especially where the use of a human generic medicine is illegal.

The VMD has reported on the trends in the reports we have received related to human medicine use and veterinary history demonstrates the fact that adverse reactions do occur when human medication has been used in animals.

An example used to challenge the VMD's advice on the use of human generics was isoflurane as an inhalation anaesthetic. This product is used as a vapour and is formulated virtually as a pure substance and so it is likely that there would be insignificant differences between active ingredients from any source. It is therefore hardly a good benchmark for other generic formulations and as a result the data required to prove equivalence is relatively simple to provide. It is important to remember that impurities present in the same active substance from different manufacturers may differ (albeit at very low levels in pharmaceutical grade products) by virtue of the different production and purification processes employed and humans and animals do not always behave in the same way when exposed to such impurities.

When considering commonly used formulated pharmaceutical products, due account has to be taken of possible differences in the chemical and physical properties of the active substance that could cause a deviation from the expected efficacy and safety of the final formulation (isomerism, crystal morphology, solubility and stability are examples). In addition, there are other excipients in formulations to consider as capable of affecting the quality, efficacy and safety of medicinal products. It is well known that small changes in formulation, be they for oral, topical or parenteral administration, can considerably affect the efficacy and safety of a medicine, as well as its shelf-life. For authorised veterinary medicines all these elements are examined during the assessment process at the VMD. We do not make assumptions about similar formulations and it is unwise for veterinary surgeons to do so.

Data Protection

A period of protection from competition is built into the European Directive, providing the opportunity for scientific innovation to be rewarded by a proportionate return on investment. Once this protection period has expired however the legislation permits competition from generic manufacturers providing they can demonstrate their product is equivalent to the pioneer product.

This is an approach applied to the authorisation of both human and veterinary medicinal products, however, pioneer products for human and veterinary use, even when based upon the same active ingredient, are assessed separately by the Medicines and Healthcare products Regulatory Agency (MHRA - the human equivalent of VMD) and ourselves.

Even though two products may quite often contain the same active ingredients or be made in the same production plant, they can and do often differ in terms of formulation. Even where they are identical product their effect in two different species can be very different. It is therefore unwise to assume that a human medicine and a veterinary medicine from the same company are identical in every way and an even larger error to assume a generic of an authorised human pioneer product will perform in the veterinary context in the same way as the corresponding authorised veterinary generic product.

Reinvestment into the veterinary sector

Commercially the veterinary and human pharmaceutical industries operate separately with the veterinary pharmaceutical market traditionally being considered as being worth around 4-5% of the human market. This separation of effort includes R&D funding where a proportion of the profits from veterinary products is used to support further innovation for the veterinary

sector. This logic extends into the negative aspect too, as human medicine profits are not used to fund veterinary medicine research. It would seem logical that the veterinary profession would wish to support its own pharmaceutical industry to maintain a future supply of novel medicines rather than undermine this effort by bypassing legitimate supply in favour of cheap, untested, human generics, a proportion of the profits of which go towards human medicine development.

Concluding statement

The Cascade is a difficult concept to implement and enforce but we try to get the right balance between animal welfare, not interfering with the clinical judgement of the veterinary surgeon and ensuring that UK authorised veterinary medicinal products are used as the default where appropriate.

There may be some areas where we are yet to find effective solutions but the application of the cascade in the UK is one of several genuine attempts to provide a wider range of medicines for the benefit of animals. We contend that effective regulation provides a significant level of assurance to veterinary surgeons by ensuring veterinary medicines can be relied upon to do what it says on the label. This can only be a secure assumption if underpinned by adequate legislation and good science.

It is recognised that the legislation does offer some support to pharmaceutical companies who provide authorised medicines and we must hope that they will continue to provide the innovations we will need for the future. Therefore utilising the assurance the VMD provides on veterinary medicines the veterinary surgeon is well placed to help animals by prescribing medicines that have a very high probability of being effective, with a secure knowledge that responsible use supports future innovation and should not lead to unacceptable risks to the animal patient, the public or the environment.

The European Legislation and the UK Veterinary Medicines Regulation and formal guidance documents can also be found on our website under 'General Information' or 'Publications'.