The Compounding Debate for Veterinary Medicines in Australia

There has been much conjecture surrounding the quality control and level of regulation with regards to compounded pharmaceuticals used in veterinary practice, heightened after the detection of testosterone (by Racing NSW) in a product promoted by the producer as better able to manage Equine Gastric Ulcer Syndrome than those suitable registered products already commercially available. This has joined a growing list of detected prohibited substances in unregistered products, with nearly every product analysed in the past 18 months containing substances other than those listed on the label as ingredients; including meloxicam, frusemide, phenylbutazone, xylazine, atropine and the aforementioned testosterone, where these substances were not known to be present and were not listed on any available labelling.

The presence of such a contaminant may very well change the way in which an active is released or interacts with an animal, potentially having serious consequences. Further, the presence of a prohibited substance that is not known to be present can have lasting implications for both a veterinarian and their client should they fall foul of the governing rules of any racing authority or regulatory body. Take the presence of testosterone from the recent example given – the Rules of Racing prohibit the administration of an anabolic steroid and carry mandatory penalties for both those guilty of administration and mandatory stand-down periods for the horse – it is not necessary for the finding of a prohibited substance in a sample obtained from the horse, only that the administration has been confirmed as occurring. This appears to be a fact that many veterinarians have been unaware of until recent times and the rise of unregistered supplements in human sport is somewhat analogous.

It is a requirement of registration of a product that impurities are reduced and that the risk of contamination is eliminated, associated with the quality of actives and the inherent quality control overseeing the manufacturing process. In a registered product the active ingredients and all the excipients must conform exactly to a standard, usually an international pharmacopeia standard. Within this standard is a list of all parameters pertaining to the chemical, reflecting all that is important to the quality and control of the active. Each active ingredient has its own specific requirements, detailing the presence of known impurities, the ratio isomers of the active and the detailed physical characteristics of the active, which will affect formulation and release characteristics.

Following the registration of a veterinary pharmaceutical, confidence is maintained in the knowledge that every batch of active constituent is analysed to ensure that it conforms exactly to the applied standard approved for that registration. This is not necessarily the case for compounded constituents, meaning that the same confidence cannot be provided. Further to this, all non-active ingredients must also comply with applicable standards. At the completion of the manufacturing process the end stage product must then comply to a final standard, meaning that time and time again, a registered product is made to conform to the same known parameters.

This process is overseen by the regulator – the Australian Pesticides and Veterinary Medicines Authority (APVMA) - meaning that the manufacturer is not solely relied upon to be compliant. The same cannot be said for a compounded product. This process is referred to as Good Manufacturing Practice (GMP) and is implemented to ensure that no cross-contamination can occur, where multiple products are being produced, owing to requirements for specific cleaning validations. It should be noted that GMP manufacturing processes are a requirement for registered products and do not apply to products manufactured by compounding pharmacists.

Additionally, the APVMA crucially require for registration that any product be subject to appropriate efficacy and safety trials, providing assurance to both veterinary practitioners and the public. This

means trials in the target species are required, including randomised controlled or bioequivalence trials. A product will only be registered if it has been suitably subjected to scientific scrutiny, being the subject of well-designed clinical trials. It is important to note that formulation changes, particularly with reference to a change in the format of a product (e.g. from liquid to paste, from tablet to transdermal etc) can ultimately result in completely different absorption profiles. Such changes require bioequivalence studies to prove that an equivalent blood level is achieved after administration, ensuring the same safety and efficacy that the veterinary industry has come to expect as standard.

Stability is also assured, given the requirement to maintain and repeatedly test three batches of a registered product for the listed shelf storage life, at set temperature and humidity for the duration.

On the basis of this brief discussion, any claim regarding a compounded product possessing the same quantity of ingredient when compared with a registered product that contains such a regulated active ingredient, is not the same and must be considered with a degree of healthy scepticism. The quantity of ingredient alone tells you very little about the possibility of the presence of impurities or contaminants and can go no way to predicting efficacy or safety of a compounded product. Compounded ingredients and registered active ingredients are simply not guaranteed to be the same.

There is no question that there is an appropriate time and place for the use of compounded veterinary pharmaceuticals. It has become increasingly common; however, for these to be used in the first instance or for financial reasons – when considering the relevant Commonwealth and state legislation – this is rarely justifiable and more often than not is not in compliance with current standards of veterinary science. Veterinarians must ensure that, when making the decision to use a compounded product, they have thoroughly evaluated all aspects of this decision – quality, financial considerations, scientific validity and professional standards. Compliance with the relevant legislation requires that a practitioner understands and has considered these aspects in detail.

Furthermore, it has become apparent that not all compounding pharmacists are aware of fulfilling their statutory obligations, particularly when in receipt of an order or written prescription from a veterinarian that is not compliant with the relevant legislation.

Considering the cost of an individual medication in isolation is not a valid assessment of the true cost of treatment, nor is it suitable justification for the use of a compounded product where a registered one is available. Beyond the price per tablet or dose, consideration should be given to the complete financial implications of treatment choices. The most obvious financial impact occurs in food and performance animals, where the potential costs associated with residue violations or prohibited substance violations can be very serious indeed. While these risks are apparently well understood by the veterinary profession, recent evidence indicates that they need to be reiterated to all participants and involved parties, with veterinarians playing a key role in mitigating and explaining these risks.

At first glance, these considerations may appear simpler in small animal practice, however, suboptimal treatment, animal welfare and drug stewardship remain key considerations, in addition to the cost borne by the owner's pocket.

Scientific validity and professional standards: The AVA guidelines on the use of compounded medications currently state "compounded medications can be used if there is no alternative registered veterinary or human medication" and go on to say that they may also be used where they are "scientifically justified". (AVA – Veterinary use of compounded pharmaceutics ratified 15 Oct 2015). Veterinarians need to set the standard for the appropriate use of the veterinary medication that they continue to be lucky to gain access to, whilst always maintaining an understanding of current

standards of veterinary practice. Veterinarians are not wholesalers or shopfronts for the provision of medications, but practitioners that use a range of skills and knowledge to make therapeutic decisions. Habit can lead to a failure to assess if the use of a compounded product is in fact a result of the absence of a registered alternative or in fact “scientifically justified”. If the decision becomes one that is not carefully made with due care and regard to all factors that relate to that decision, then the professional standards that veterinarians hold themselves may be undermined.

So, the devil is in the detail. There is a time and a place for compounded products, but veterinarians need to be sure that, when making decisions on the use of compounded products they are thoroughly evaluating all aspects of this decision and that they are making scientifically informed and valid decisions that uphold the standards of the profession in line with their legislative obligations.