

“WHY DO VETS PRESCRIBE NON APVMA REGISTERED MEDICINES?”

A companion animal perspective

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Introduction

In Australia the federal regulator of veterinary medicines is the Australian Pesticides and Veterinary Medicines Authority (APVMA). The APVMA administers the Agvet Code which is scheduled to the *Agricultural and Veterinary Chemicals Code Act 1994*. This is actually state law, though it is created and amended by the Commonwealth. There are also state and territory laws dealing with supply and control of use of veterinary medicines through the poisons/therapeutic goods legislation in all states^{1,2}. This paper will deal with the evidence used to make prescribing decisions rather than the complexities of the laws.

The regulation of agricultural and veterinary chemicals is currently under review through a Ministerial Partnership between the Minister for Agriculture, Fisheries, and Forestry and the Minister for Finance (for the APVMA legislation) and through a Council of Australian Governments (COAG) process (for the control of use aspects), with proposals for legislative change both at the federal³ and state levels⁴. It is hoped that the outcome will be a more understandable and harmonised system.

From a sustainability perspective, the correct prescribing decisions are vital for successful veterinary practice management, maintaining animal welfare, and continuing success of allied companion animal industries, as well as maintenance of veterinary prescribing rights.

Current veterinary prescribing practices

Veterinarians face the dilemma that our patients are different species, sizes and difficulties to medicate. The Australian Animal Health industry is a relatively small market within the pharmaceutical world (or extremely small e.g. non-poultry birds, exotics and pocket pets). This may reflect in fewer veterinary medicines being imported into Australia (or developed here) and registered. It can also result in a relative higher price point of registered medicines, since registration incurs significant cost to the pharmaceutical company. Registration is undertaken via full cost recovery by the APVMA.

Veterinarians today may seek to use cheaper human medications, both approved by the Therapeutic Goods Administration (TGA) and unapproved, for “off-label” prescribing. In the

¹ APVMA factsheet on Veterinarians and Veterinary Medicines, www.apvma.gov.au/publications/fact_sheets/docs/veterinarians.pdf

² AVA compounding policy Feb 2010 www.ava.com.au/policy/27-veterinary-use-compounded-pharmaceuticals

³ DAFF Ag-Vet reform www.daff.gov.au/agriculture-food/ag-vet-chemicals/better-regulation-of-ag-vet-chemicals

⁴ COAG Review of Chemicals and Plastics Regulation www.daff.gov.au/agriculture-food/ag-vet-chemicals/domestic-policy/psic

USA where the veterinary medicines spend is around US\$3.5B; it is estimated only 1/3 of all medications used in animals are registered by the Food and Drug Administration FDA (1). Indeed the recent demand for compounded veterinary medicines in companion animals has been driven by veterinarians wishing to access a greater range of human and veterinary medicines, smaller animal user friendly formulations and also access to cheaper medicines for the individual patient.

Cost should not be the main consideration in our prescribing decisions. Rather it should be efficacy and safety, otherwise there is no benefit to the patient and so cost effectiveness is a false premise. A recent review, of what UK clients (2) valued from their veterinarian, focused on knowledge and ability to communicate information ahead of cheap fees or medicines. If we prescribe an unregistered veterinary medicine this needs to be supported by counselling so that informed consent is given by the owner.

In order to explain the risk-benefit, we must be aware of the current level of evidence. Few meta-analyses (the highest form of evidence) exist in veterinary companion medicine. Randomised controlled clinical trials tend to have small numbers and there is a lag until reports are published, if at all. We often only read the marketing information provided by the company or anecdotal case study reports from clinicians. In the case of compounding there may be a lack of comparability of one prescription to the next (as they are not batched), making a clinical trial or series of clinical case reports difficult to interpret. Thus it requires an individual clinical assessment by the veterinarian to determine if the compounded prescription is working in their patient (3, 4) e.g. through therapeutic drug level monitoring. This may incur additional cost to the owner of the animal and make therapeutic decisions difficult. It is a recommendation in the compounding guidelines of the American Veterinary Medical Association (AVMA)⁵ to only use compounded medicines where this monitoring is possible.

There are few studies of our prescribing practices. Clinical audits have begun overseas e.g. in the UK via the RCVS. These will contain important information in areas such as antibiotic use; to identify prescribing/use pressure that may give rise to antibiotic resistance. In Australia, the Australian Infectious Diseases Advisory Panel (AIDAP)⁶ is looking at this issue and will seek eventually to produce best-practice guidelines. It is in antibiotic prescribing where we most rub shoulders with our medical counterparts. With the scarcity of development of new antibiotics, the current antibiotics are precious and need to be intelligently used (5). From an OH&S and client safety viewpoint resistant bacteria carriage on companion animals has been associated with strain transference to veterinarians (6), within the veterinary hospital environment (7) and within the families associated with animals (8).

a) Prescription, supply and dispensing

As a profession we have been entrusted with prescribing rights that enable us to **prescribe and dispense** veterinary and human medications to non-human animal species.

This is a complex process, involving prescribing rights, responsibilities and required knowledge relevant to each part of the process:

⁵ AVMA Policy Compounding www.avma.org/issues/policy/compounding.asp

⁶ Pfizer Animal Health Australian Infectious Diseases Advisory Panel www.aidap.org.au

- i. Laws and guidance exist for prescribing, dispensing, labelling and information provision⁷. Of notable mention is the ability of veterinary supplied medications to be misused by individuals e.g. anabolic steroids, psychotropic drugs, and pain relievers and euthanasia solutions. While accidental human consumption is considered in APVMA registration requirements with respect to labelling and package inserts, specific human therapeutic contraindications (an unintended use) is not. Vice versa for human medications supplied to veterinary patients. In some situations little or no information may be supplied with the prescription e.g. some human drugs and veterinary drugs dispensed from bulk into alternate non-approved packaging and some veterinary compounded products.
- ii. Patient specific factors (the species' physiology/anatomy), the disease, co-morbidities, concurrent medications, known adverse drug reactions/allergies, age, reproductive stage, etc (9).
- iii. Pharmacological factors: the chemistry, clinical pharmacology relevant to the dose and dose form and if it is APVMA registered or permitted, all influence treatment selection. If unregistered and a human medication source is available then it should be TGA approved. Either the APVMA or the TGA registration number will appear on the packaging and the insert. If a compounded product is required then the quality of the compounding source needs to be considered and evaluated by the veterinarian, as this is not the remit of any regulator at present. This is being reconsidered in the current legislative reform agenda. Naturopathic, herbal and homeopathic remedies should be APVMA (and/or TGA) listed. Furthermore if one is prescribing an "off label" human medication, you must have scientific evidence related to the pharmacokinetics and the pharmacodynamics of the medicine, which in turn determines the safety, and efficacy of the prescribed dose and formulation in the patient's species (9).
- iv. Pharmaceutical factors: When dispensing a registered human or veterinary medication from your dispensary, it must be in-date and stored to correct stability conditions. These have been assessed and are stated on the label/insert of the APVMA or TGA registered product.
- v. Storage: The wholesalers need to authenticate the source of the product, and ensure correct carriage on route to the practice e.g. refrigerated courier delivery; otherwise stated stability will not be ensured. Also of consideration is the transport mode from dispensary to the patient.
- vi. Dispensing: a veterinary compounded product supplied by a pharmacy from your dispensary is in fact a 3rd party user or on-seller arrangement i.e. the pharmacist is not dispensing it directly to the user, upon your prescription. So the above (iv,v) factors hold true. However it can only be based on the information provided by the compounder and consideration needs to be taken that any stability information (if provided) has not been independently verified, may vary from prescription to

⁷ AVA guidelines for prescribing, authorizing and dispensing veterinary medicines 2005
http://www.ava.com.au/sites/default/files/documents/Other/Guidelines_for_prescribing_authorising_and_dispensing_veterinary_medicines.pdf

prescription, methodology may not be validated or standardised and is not a regulated process⁸. This would be true also for information concerning maintenance of sterility in the case of multi-use injectables and eye preparations once opened.

- vii. **Monitoring:** The outcome and aftercare is important particularly with respect to reporting of adverse drug reactions to the manufacturer or compounder and to the APVMA through the Adverse Experience Reporting Program (www.apvma.gov.au/qa/aerp.shtml), in any case where an unexpected or adverse reaction to a drug (ADR) may have occurred. Although reporting of ADRs for compounded products is not mandated, it allows improved compounding practice and alerts a higher body if there is an issue. This includes when a medication hasn't worked appropriately as well as toxicities e.g. vaccination failures, unexplained sub-therapeutic drug levels, poor dynamic drug response testing and when resistance is expected in the case of important antibiotics.

b) Registered and unregistered veterinary medicines

In our opinion, regulation (i.e. state and federal harmonisation of legislation) and professional standards (e.g. state veterinary surgeons boards registration and codes of conduct and policies from professional bodies e.g. AVA and AVMA), help to prevent or limit disasters in the prescribing area. They also allow assurance to the animal health industry and businesses both in the traditional manufacturing, wholesaling areas and the newer veterinary compounding area.

Companion animal products would be regarded by the APVMA as low risk in that they do not pose food and trade risks. The data requirements for companion animal products are therefore less, but they get the same treatment in regard to other risks such as harmful to humans, animals, plants or things, or to the environment. The regulatory dossiers that are approved by the APVMA have a numbers of parts - chemistry of the active constituent and formulation, formulation stability, safety to the animal, people and the environment (e.g. skin residues, urinary and faecal excretion) and efficacy. This represents years of expensive research by the company and in order for the product to be approved, the data must be generated to a high standard. The APVMA further limits this risk by ensuring that the manufacturers who manufacture this medicine do so to a quality level called Good Manufacturing Practice (GMP). Once a medicine is approved it is given an APVMA registration number that appears on the label. Any changes to that drug require resubmission to the authority including different dosages and dose forms, new label claims, changes in particle size and source of the active chemicals and excipients, and change in the manufacturing process or site of manufacture. Post marketing studies and adverse event reporting help ensure continuing safe use.

For lower use, lower risk or emergency use the APVMA may consider granting a permit rather than full registration. The APVMA must be satisfied of various matters that relate to efficacy and safety of a permitted product dependent on argument provided by the manufacturer rather than a full dossier provided as for a registered product. It must clearly say on the label that this is the case. As prescribers of a permitted product we supply a prescription to the wholesaler who in turn supplies a copy to the manufacturer and keep a copy on file for APVMA audit purposes. We need to explain to the owner that this is a

⁸ www.veterinarypracticenews.com/vet-cover-stories/the-value-of-fda-approved-drugs.aspx

permitted and not a registered product. The reasons for permit issue are varied e.g. emergency use for the Equine influenza vaccine; research permit and minor use permit (www.apvma.gov.au/permits/veterinary/index.php). If use increases then the manufacturer will be asked to fully register the product.

For unregistered medicines, to understand the risk (and therefore potential liability) we need to self-evaluate the evidence in the areas discussed above (where and if it exists). We also need to be aware if we are legally able to prescribe such medicines.

From a prescribing risk for unregistered medicines we need to consider that:

- Some manufacturers can act illegally and not register their products for animal use even though they state animal use claims on their labels and marketing material.
- Compounding is exempt from control by the APVMA. This confusion is currently being examined by a working group within the Pharmacy Board of Australia⁹ and within the APVMA and DAFF. There is a draft APVMA information sheet of best veterinary compounding practice from a production and education perspective that will be finalised and accessible at www.apvma.gov.au by the time of this conference. This is being compiled by an APVMA-industry working group.
- Some manufacturers/compounders may import/use active ingredients which may be sub-standard or from changing sources that affect the quality and reliability of the product.
- Some distributors illegally import unregistered product.
- It is appropriate to alert your clients or a referring veterinarian of the illegality in accessing overseas medication via the internet, without an appropriate APVMA import consent. Import consent is required for the importation of all unapproved active constituents and all unregistered products. However, the APVMA will not give consent to the import of an unregistered product after a veterinary chemical product containing the same constituents and bearing the same or similar name has been registered in Australia.
- Owners may access internet advertised medications without professional input. This is difficult to control, but we should actively counsel against this behaviour. No APVMA consent is issued to owners wishing to import unregistered products and there is likelihood that the product may be stopped by Customs. The legal alternative is for the owner to ask you to apply for an APVMA Consent to Import and import on their behalf. It is up to you to use your professional judgement in deciding if the use of an unregistered product is preferable for your patient. The APVMA website provides advice on this issue; www.apvma.gov.au/supply/import.php.

c) Pharmacist veterinarian interactions

Medical doctors only prescribe to one species with generally a second tier of oversight and safety occurring at the level of the pharmacist. Pharmacists are educated to dispense to humans, with perhaps at best a couple of lectures on veterinary pharmaceuticals. They do receive general training in compounding practice but there is a push to have an advanced certificate of pharmacy-compounding that addresses more complex issues. In the main veterinary compounding is carried out by pharmacists not veterinarians.

⁹ Communique Pharmacy Board of Australia Nov 2011 Compounding Working Party, www.ahpra.gov.au

Traditionally pharmacists have had little training in animal physiology with respect to species differences (in drug metabolism, efficacy and safety) nor in veterinary related law. Therefore the responsibility rests with the veterinary prescriber. The veterinarian does not tell the pharmacist what to include in a compounded formulation rather the pharmacist accesses this information from a formulary. Education of pharmacists is one of the key pillars recommended by the APVMA working group to improve veterinary compounding practice. In the USA there is a whole new curriculum evolving in this area (10) as well as professional organisations to help self regulate and improve the industry.

Veterinary compounding is not regulated by the TGA. Compounding of human medications is regulated by the TGA; if it is considered to be **extemporaneous manufacture** Class 3, requiring a TGA license. In the TGA compounding regulatory framework [NCCTG 2008] response June 2010, it is noted compounding:

- Class 1 (individual products for **immediate supply to meet the identified needs of an individual patient**) and
- Class 2 (sufficient quantities of product to meet the anticipated needs of patients, **with supply from that pharmacy**)

shall continue as self assessment or other, as required by pharmacy regulators or professional associations. No changes from current controls are proposed with respect to advertising (i.e. **no to consumer advertising of S4, S8 or most S3 medicines**)¹⁰.

The AVA Therapeutics Advisory Committee has suggested an inter-professional discussion with the Australian professional pharmacy bodies such as the **Pharmaceutical Society of Australia (PSA)**. This has not yet eventuated at time of press. The PSA have standards around human use but seem to provide limited guidance for their members on veterinary use. For humans they state: "Compounding is the preparation and supply of a single unit of a product intended for immediate use by a specific consumer". The pharmacist must ensure product quality when compounding a product. Compounding occurs when the prescribed formulation or a suitable alternative cannot be obtained commercially. Commercial products are preferable to compounded products because they are reliably subject to formal quality control procedures.^{11"}

Pharmacies, including compounding pharmacies, must be owned by registered pharmacists. In Australia pharmacists are registered by the Australian Health Professional Regulatory Agency's Pharmacy Board of Australia. Pharmacists are trained in the science of the formulation and stability of the pharmaceutical required to produce a product- these can be used for veterinary or human use. They are not trained in animal physiology or biochemistry. They are required to comply with all legal limitations around poisons and scheduled medicines regardless of species. These are covered in the Poisons Acts of each state.

Veterinary registration is state and territory based and so it is difficult to know how that affects the relationship of veterinarian-pharmacist-patient in the trio of prescription-supply-dispensing with respect to liability issues. In the main, how it currently operates with veterinary compounding: the veterinarian still acts as prescriber and dispenser with the pharmacist supplying to the veterinarian's pharmacy (dispensary) for on sale to the client. So, in the case of a suspected ADR since a compounded prescription is not batched, the

¹⁰ www.tga.gov.au/newsroom/consult-ncctg-compounding-100610.htm#att

¹¹ Pharmaceutical Society of Australia, professional Practice Standard, Version 3, 2006

whole of the script will have been couriered to the veterinarian then to the patient, making analysis of a faulty product versus supply/dispensing problem very difficult to discern.

Pharmacy dispensing guidelines are silent on veterinary compounding. However revisions are pending and will include a review of compounding¹²: “Both simple extemporaneous preparation and compounding by pharmacists are currently exempt from the Code of Good Manufacturing Practice when appropriate poisons legislation is observed. Also, both must be done after consultation by the pharmacist with a client or on the prescription of a registered health practitioner or veterinarian for an individual client or animal. There is no exemption for the making of batches or for bulk supply for surgery or veterinary use. Supply to another pharmacy for re-labelling is considered manufacturing. Proposed guidelines being drafted by the working party for consideration by the Board seek to clarify these issues for pharmacists.”

Looking forward, new regulations require careful consideration, education, and ongoing advice and monitoring by all parties. In the USA there is currently before the courts an appeal from the FDA over prosecution of Frank’s Compounding Pharmacy for illegal compounding¹³, in relation to veterinary compounding matters. This was originally dismissed by the court. Adding to his list of criticisms, the judge aired concerns about the FDA’s “maximalist” use of current laws in an attempt to enjoin compounding, rather than map new, comprehensive regulations regarding the practice.”¹⁴ It would appear that this may be good advice to follow for our regulatory bodies.

Conclusion: It is important to remember that our prescribing rights are linked to our veterinary registration and abuse of these rights or unprofessional conduct with respect to these rights could lead to withdrawal of our registration and a professional liability claim. As the legislation is currently under review we need to keep abreast of change, maintain our evidence based knowledge and best practice education and comment when there is a need for a stakeholder viewpoint.

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¹² November 2011 Communique PBA www.pharmacyboard.gov.au/documents

¹³ Veterinary Compounding Out Of FDA’s Jurisdiction, Judge Rules, Jennifer Fiala VIN News Service September 13, 2011

¹⁴ FDA files notice of appeal over veterinary compounding ruling Nov 18, 2011 By: Rachael Whitcomb, DVM NEWSMAGAZINE <http://veterinarynews.dvm360.com/dvm/Veterinary+news>

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