The Delicate Arrangements of Off-label Use of Medication

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Introduction

First and foremost I would like to emphasise that I possess no qualifications in law, and offer the following opinions and comments in the most general of terms of a private, general accession practitioner trying to stimulate discussion about the ethical use of off-label medications within the framework of the current legislation.

Resources

Both in preparation of this short presentation and in the management of my small business I have found the following resources invaluable:

- The website of the Veterinary Surgeons Board in NSW
  http://www.vsb.nsw.gov.au/ - there are links on this site to each of the states

  It is exceedingly interesting that there are 16 different pieces of legislation (and some case law) which impinge directly on the day to day running of veterinary practice in NSW! These can all be accessed through the VSB site above.

- The website of the Australasian Legal Information Institute
  A joint facility of UTS and UNSW Faculties of Law
  http://www.austlii.edu.au/

- And, of course, the website of our wonderful and auspicious organisation, especially the page in the policy compendium
  http://www.ava.com.au/member.php?showpage=334&ctrail_add=Prescribing%20&%20Dispensing%20Guidelines#27
  which about halfway down has a section "22.5 'Off-label' use" which I have thoughtfully copied below to facilitate discussion:

22.5 'Off-label' use

'Off-label' prescribing is writing a prescription or authorisation to a client to allow them to use a registered drug or veterinary chemical in a manner outside the range of uses permitted by the approved label directions - including species of animal, dosage, treatment interval etc. (but not contrary to a specific label restraint - see section 22.6).

Veterinarians are permitted to exercise professional judgement in the 'off-label' use or supply of most drugs or other veterinary medicines. This gives veterinarians access to beneficial drugs which may be registered for human use or which have limited registration for veterinary use. However, veterinarians must be aware that access to such drugs is the subject of concern in the community, and that misuse of such drugs may lead to withdrawal of this authority.

Legal limits

A number of legal limits have been placed on the 'off label' prescribing of drugs by veterinarians under national control-of-use principles adopted by most states and territories. These primarily relate to treatments for defined food-producing species (excluding horses), and are less stringent for companion animals. In most jurisdictions use of any product for companion animals is permitted, but supply for their treatment is usually restricted to human pharmaceuticals or products compounded by the veterinarian or on the veterinarian's prescription.

These limits generally include:

- A ban on the use of unregistered products, including agricultural chemicals, to treat food-producing animals, with the exception of single animals. (Definitions of which animals are food-producing vary by jurisdiction and relevant legislation or orders should be consulted.);
- A limitation on 'off-label' use, prescribing or authorising for food-producing animals of drugs and other veterinary chemicals unless they are already registered in at least one major food producing species;
- A ban on use (or prescription/authorisation) contrary to any instructions under a "Restraint(s)" heading on a product label – see section 22.6;
- A requirement to ensure all treated animals are adequately identified, sufficient to last until the expiry of any relevant withholding period;
- A ban on formulating, dispensing or using a veterinary chemical, registered for oral or external use, as an injection.

[In Queensland, if there is no 'major trade species' (which includes any food producing animals) listed on the label, only a single major trade species animal may be treated 'off-label'. For animals other than major trade species, registered products can be used 'off-label'.]

Food producing animals

Specific drugs for which there are 'off-label' restrictions in food-producing animals include:

- *Chloramphenicol* to treat any food-producing animals, including horses; § Diethylstilboestrol in livestock;
- *Virginiamycin* - [It has been proposed that use as a growth promotant be prohibited, and its therapeutic or prophylactic use in food-producing animals limited to 21 days in any chicken broiler flock and 28 days for cattle and sheep treatment in any 12-month period. Veterinarians should check the current situation.];
- *Phenylbutazone* - Not recommended for use in cattle due to persistence in tissues, and consequent residue problems;
- *Triclabendazole* - Not recommended for use in lactating dairy cows, unless milk can be withheld from human consumption for an extended period. In most jurisdictions, this use is a specific restraint, and therefore prohibited.
- *Aminoglycosides* (gentamicin, neomycin, streptomycin) - Sequestration in kidneys, with consequent residue or toxicity problems.
- *Sulphonamides* - Parenteral administration of potentiated sulphonamides can produce high tissue levels, with consequent risk of residues. § Colloidal silver - Not registered as a treatment for mastitis.
- Many companion animal antibiotics contain specific label prohibitions against use in food producing animals and these restrictions must be observed (other than for single animals).

A range of other restrictions apply in each jurisdiction and the relevant state/territory legislation should be consulted – see section 32.

The veterinarian assumes full responsibility for the use of any drug contrary to the drug's registered use pattern as reflected on the manufacturer's label. If using drugs in any manner outside the range of uses permitted by the manufacturer's label or product insert, it is essential to inform the client of this, the

reasons for the choice of drug, any other options available to the client and to document the informed consent of the client in the clinical records.

Use of unregistered chemicals or human medicines in food-producing animals should be limited to those cases where appropriate veterinary drugs do not exist or where they are known, or can reasonably be anticipated to be, ineffective. Legislation in most jurisdictions restricts such treatment or supply to single animals only – Consult the relevant legislation for the local definition of 'single animal'. It is unacceptable to use a human medicine for common disease conditions in food-producing animals where approved veterinary drugs e.g., antibacterials, anti-inflammatory agents etc, are available. **A veterinarian assumes full responsibility when an unregistered chemical or human medicine is used rather than a registered veterinary medicine.

'Off-label' use in food-producing animals should only be considered when:

- a careful diagnosis and evaluation of the condition for which the drug is to be used has been made;
- the veterinarian is operating within the bounds of a valid veterinarian-client relationship;
- a deliberate determination is made that there is no other appropriate veterinary drug available, ie. there is no marketed veterinary drug specifically labelled for the disease condition to be treated or the veterinary drug has been found clinically (or in laboratory tests) to be ineffective by the veterinarian in the animals to be treated;
- in the case of food-producing animals, adequate steps to prevent the occurrence of illegal residues in edible animal products have been taken. This should include a review of the best available toxicological and tissue distribution and tissue residue depletion data and establishment of an appropriately long withholding period, to ensure that no detectable residues will occur. The animal owner or manager should be given explicit written withholding period instructions, and the veterinarian should be very confident that these instructions will be faithfully followed. Where a long withholding period is provided, to ensure no residues will remain, this period should also be satisfactory as an export slaughter interval.
- the drug has been approved for use in at least one major food-producing species (for other than single animals).

Important! Some form of regulatory action may still be considered by state/territory authorities when an illegal residue occurs even if a veterinarian has followed these precautions. As indicated above, when unregistered (veterinary) chemicals are supplied, or registered chemicals are used 'off-label', the veterinarian is legally responsible if the withholding period specified on the label supplied by the veterinarian proves to be inadequate.

While veterinarians are not usually held responsible by authorities controlling residues detected in competition animals, they should understand that the livelihood of a client can be affected if such residues are detected.

The veterinarian also assumes full responsibility for complying with the conditions of use of experimental drugs or those sold under APVMA permits . It is imperative that the veterinarian adheres to the PAD checklist criteria when using or supplying these drugs and does not on-sell these drugs to any person except the client who is the owner or custodian of the recipient animal. These drugs must not be repackaged or relabelled from the manufacturer's specifications, however the dispensing veterinarian should affix a dispensing label as described for Schedule 4 drugs. All permit conditions must be followed.

['Off-label' use of non-restricted medications in food producing animals by owners, eg. drenches used contrary to label directions, is illegal and should be actively discouraged.]

Issues

- we are relatively fortunate in exotic practice to have few situations where withholding periods are going to be critical to international trade, though examples of some of our patients, such as small ruminants, rabbits, or poultry, could well end up in the human food chain by its very nature exotic animal practice is going to generate a lot of off-label dispensing, because there is so little medication labelled for use in these species
- the first 3 things to do to prevent legal complications of extra-label drug use IMHO are communicate excellently, communicate clearly, and communicate thoroughly.
- the next thing to do as make accurate contemporaneous medical records
- the fifth (is that what I am up to?) thing is to make sure you are up-to-date with the standards of your peers by adequate professional development or continuing education. Whether you are using medications as per label or off-label you are markedly more likely to run foul of the legal aspects if you don't know what you are doing. A scan of the reasons for complaints to be lodged with the NSW VSB include many medicating-related ones. Only very few are directly associated with off-label use, and all of these are clearly where an average veterinarian (like me) should know the medication was inappropriate. I feel certain that these complaints would not have eventuated had the veterinarian involved maintained their professional development through continuing education, and in each case the VSB has almost invariably recommended CE as part of the remedy
- the final thing that I think we should do is be aware of the various legislative requirements and mandates that we operate under. The web page of the NSW VSB mentioned above does list these, and there are some useful links, including to the NSW Department of Health - Pharmaceutical Services Branch "Guide to Poisons and Therapeutic Goods Legislation for Veterinary Surgeons". This PDF document is important reading for all NSW veterinarians.

  While the Veterinary Surgeons Act, Poisons and Therapeutic Goods Act, Stock Medicine Act, and Drug Misuse and Trafficking Act all have aspects that impinge a veterinarian's actions in prescribing medications, we should also be aware of the Australian Pesticides and Veterinary Medicine Authority (see http://www.apvma.gov.au/). Formerly known as the National Registration Authority, this is the Commonwealth Body that would have an interest in any medications that entered the human food chain. I believe Mike Cannon is going to review a presentation by Dr Lee Cooke of the APVMA that was made at the AVA National Conference in May, where many useful facts were highlighted. The APVMA website is also an important one for the reporting of adverse events - unfortunately if we use medications in unusual circumstance we are more likely to see adverse events and we should take the time to report these for the benefit of others.

Mark's Hypotheticals

Should we get people to routinely sign some type of consent form? Definitely not, in my opinion:

* It is my understanding that consent forms of this type rarely stand up in legal institutions, because the client lacks the knowledge base, even with my erudite explanation, to provide informed consent; and
* as well this simply places the whole process on a legalistic, litigious basis at the first instance, and makes it more likely clients will pursue a litigious course if they are not happy with an outcome.

I do, however, think that a note in the record that the off-label nature of the therapy (including risk) is discussed, understood, and accepted by a client. There are some higher risk situations (especially with antineoplastics and some analgesics) where I do indulge in the "consent form".

Are backyard chickens a special situation? The short answer is yes! What I do about it at my hospital is to now prescribe only those medications registered for use in poultry to backyard chicken flocks, except in exceedingly special circumstances. I can easily imagine a scenario where a new flouroquinolone resistant strain of Salmonella kills a young child, and investigations by the health department identify inappropriate antimicrobial therapy by a veterinarian as the material cause, with all the horrendous implications that would entail. And I don't want it to happen to me!

Conclusion

The one critical element in the debate about off-label medications I have not touched on is responsibility. If we accept the privilege of determining novel uses for the many medications we are lucky to have access to, then we must accept the responsibility of communication, appropriate medical record keeping, awareness of our legislative responsibilities, and ongoing professional development to stay abreast of best practice in using these medications. When we do all of these things, the possibility of legal ramifications of significance, I think, is remote.

Review Questions

The most important part of off-label medication use is an appropriate disclaimer. True or False.

Exotic pet practice is insulated from extra-label use of medications because there are so many medications labelled for use with these animals. True or False.

Who accepts responsibility for off-label drug use?

Australian Veterinary Surgeons Boards

ACT	
Registrar Ms Kathryn Kelly Veterinary Surgeons Board of ACT PO Box 976 CIVIC SQUARE ACT 2608	Phone (work): (02) 6205 1599 Fax: (02) 6205 1602 Email:vsbregistrar@act.gov.au Web: http://www.health.act.gov.au/c/health?a=da&did=10033300
NEW SOUTH WALES	
Registrar Glenn Lynch 55 Portman Street GREEN SQUARE NSW 2020 PO Box 6391, Alexandria, NSW 2015	Phone (work): (02) 9699 4477 Fax: (02) 9699 4488 Email: registrar@vsb.nsw.gov.au Web: http://www.vsb.nsw.gov.au/
NORTHERN TERRITORY	
Registrar Veterinary Board of the Northern Territory Department of Primary Industry & Fisheries GPO Box 990 DARWIN NT 0801	Phone: (08) 8999 2133 Fax: (08) 8999 2043 Email: karen.richardson@nt.gov.au
QUEENSLAND	
Wayne Murray Registrar Veterinary Surgeons Board of Queensland GPO Box 46 BRISBANE QLD 4001	Phone (work): (07) 3239 3600 Fax: (07) 3239 3510 Email: vsbqld@dpi.qld.gov.au Web: http://www.vsb.qld.gov.au/
SOUTH AUSTRALIA	
Registrar Ms Sue Millbank Veterinary Surgeons Board of SA Suite 13 70 Walkerville Terrace (PO Box 218) WALKERVILLE SA 5081	Phone (work): (08) 8269 3216 Fax: (08) 8342 5325 Email: vsbsa@senet.com.au Web: http://www.vsbsa.org.au/
TASMANIA	
Registrar Veterinary Surgeons Board - Tasmania PO Box 183 HUONVILLE TAS 7109	Phone (work): (03) 6239 6823 Fax: (03) 6239 6824 Email: vsbtas@ava.com.au Web: http://www.dpiwe.tas.gov.au/inter.nsf/ThemeNodes/EGIL-5D78W3?open
VICTORIA	
Registrar Miss MB Wilson ACIS The Veterinary Practitioners Registration Board of Victoria Level 11 470 Collins Street MELBOURNE VIC 3000	Phone (work): (03) 9620 7444 Fax: (03) 9620 7044 Email: registrar@vetboard.vic.gov.au Web: http://www.vetboard.vic.gov.au/

Australian Veterinary Surgeons Boards (Continued)	
WESTERN AUSTRALIA	
Registrar Andrew Keefe Veterinary Surgeons Board of WA 28 Charles Street (PO Box 1124) SOUTH PERTH WA 6951	Phone (work): (08) 9367 4674 Fax: (08) 9368 2193 Email: vsbperth@wt.com.au Web: http://www.vetsurgeonsboardwa.au.com/

A Guide to Poisons Schedules

Classification: Drugs and poisons are classified according to the Schedules in which they are included. The following is a general description of the Schedules. For the legal definitions, however, it is necessary to check with the relevant State or Territory authority.

- *Schedule 1*. This schedule is intentionally blank.
- *Schedule 2*. **Pharmacy Medicine** - Substances, the safe use of which may require advice from a pharmacist and which should be available from a pharmacy or, where a pharmacy service is not available, from a licensed person.
- *Schedule 3*. **Pharmacist Only Medicine** - Substances, the safe use of which requires professional advice but which should be available to the public from a pharmacist without a prescription.
- *Schedule 4*. **Prescription Only Medicine**, or **Prescription Animal Remedy Substances**, the use or supply of which should be by or on the order of persons permitted by State or Territory legislation to prescribe and should be available from a pharmacist on prescription.
- *Schedule 5*. **Caution** - Substances with a Iow potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.
- *Schedule 6*. **Poison** - Substances with a moderate potential for causing harm, the extent of which can be reduced through the use of distinctive packaging with strong warnings and safety directions on the label.
- *Schedule 7*. **Dangerous Poison** - Substances with a high potential for causing harm at Iow exposure and which require special precautions during manufacture, handling or use. These poisons should be available only to specialised or authorised users who have the skills necessary to handle them safely. Special regulations restricting their availability, possession, storage or use may apply.
- *Schedule 8*. **Controlled Drug** - Substances which should be available for use but require restriction of manufacture, supply, distribution, possession and use to reduce abuse, misuse and physical or psychological dependence.
- *Schedule 9*. **Prohibited Substance** - Substances which may be abused or misused, the manufacture, possession, sale or use of which should be prohibited by law except when required for medical or scientific research, or for analytical, teaching or training purposes with approval of Commonwealth and/or State or Territory health authorities.

Internet Law Sites

http://www.austlii.edu.au	Most Australian databases. Statute law, regulations, court cases, NSW State Awards
http://www.lawportal.com.au	Similar, easier to use
http://www.scaleplus.law.gov.au	Federal Law database, some States also
http://www.law.gov.au	Federal Attorney-General - links to many law databases
http://www.legislation.nsw.gov.au	NSW legislation database. Up to date and accurate
http://www.industrialrelations.nsw.gov.au	NSW Office of Industrial Relations
http://www.thelaw.tas.gov.au	Tasmanian legislation
http://www.wagenet.gov.au	Information about wages and conditions
http://www.hreoc.gov.au	Federal anti-discrimination matters
http://www.lawlink.nsw.gov.au/adb	NSW anti-discrimination database
http://www.asic.gov.au	Australian Securities and Investment Commission. Company information, forms to register company, banned names list, etc
http://www.itsa.gov.au	Insolvency trustee service Australia - bankruptcy
http://www.ato.gov.au	Australian Taxation Office
http://www.workcover.nsw.gov.au	NSW Workcover Authority
http://www.fairtrading.nsw.gov.au	NSW Dept of Fair Trading - partnerships, consumer protection, co-operatives, REVS and more.
http://www.epa.nsw.gov.au	NSW Environmental Protection Authority
http://www.rspca.org.au	RSPCA