Compounding of drugs for veterinary use
V Naidoo [BVMCh, MSc (Vet), PhD]
Department of Paraclinical Sciences, Faculty of Veterinary Science, University of Pretoria

Introduction
The practice of the veterinary profession is highly dependant on the use of commercial veterinary remedies. While a large number of these drugs are currently available as either stock remedies or veterinary medicines, the drugs available do not cover the entire spectrum of therapeutic agents required in the management of animal disease. Whilst a number of different factors may be responsible for the absence of required medication, the most common has to do with the size of the veterinary market i.e. the local market is not large enough to support the sale of these remedies.

As a result of the non-availability of veterinary remedies, veterinarians have been afforded the privilege to use drugs extralabel, which essentially allows one to use non-registered drugs for animal use in South Africa. While in the main, this implies the use of human medication in animals, this also encompasses the process of drug compounding. In addition to non-availability mentioned above, other factors that favour compounding usually include an inability to obtain correct dosage forms e.g. only tablets available when oral solutions may be required, or when current dosage concentrations are too high to safely allow for use in small animals.

What is Drug Compounding?
Compounding is a veterinary privilege afforded by the Medicines and Related Substances Control Act (Act 101 of 1965). Whilst the Act does not strictly define compounding, this process may be defined as the manipulation of an available medicines or pure chemical substances to obtain a new dosage form. In the case of registered medicines this would also include any product manipulation that results in alternate instructions other than that already provided on the approved drug packaging. As such veterinary compounding may be simply defined as the self preparation of a medicine for animal use such as the formulation of a new veterinary medicine from self-sourced raw material and/or the reformulation of an available remedy viz. drug dilution, crushing of tablets into food, mixing of drugs for wildlife capture, etc. In addition, as vets we not only have the privilege of being able to compound drugs in house, we may also instruct a pharmacist to compound on prescription.

The legalities of registered medicines
As in almost every country in the world, drug availability is highly regulated. This is important as the registration process ensures that commercial products are of adequate quality, safety and efficacy:

- **Quality**: Most drugs are mixture of chemicals with the exception of the newer high molecular weight protein drugs like erythropoietin. None the less, despite the source of the product, medicines are produced by manufacturing companies under laboratory or factory conditions. As a result of the production process, it is possible that foreign contaminants such as endotoxins or other foreign chemicals
could inadvertently enter into the final raw or finished product thereby resulting in an inferior and possible hazardous medicine e.g. the recent contamination of pet food with cyanuric acid/melamine highlighted the dangers of this process. Therefore to ensure the quality of manufactured product, every aspect of drug production is strictly controlled by the quality process known as Good Manufacturing Practice (GMP).

- **Efficacy:** Drug formulations are complex mixture of active and inactive ingredients. As a result of these differences, formulations with the same active ingredient may not necessarily produce the same effect as their inactive may well differ e.g. medical oral clavulanic formulations are not considered equivalent to the veterinary formulations. As a result of this well understood pharmaceutical factor, every formulation has to be extensively tested prior to registration. While for new chemical entities (NCE) this would entail exhaustive studies in a few hundred animals, the pharmaceutical alternative/similar products (generic products) may be registered based on strict bioequivalence guidelines. As a result registered products are usually effective in 80% of the recommended target population (Natural population variation), at the recommended dose barring external factors such as microbial resistance.

- **Safety:** Since different formulations are manufactured by different companies, they will always to some extent differ. With these differences lying mainly in the specific combination of active and inactive ingredients, every formulation has to be initially tested for its potential to be toxic, irritant or harmful in the target population (Target animal tolerance studies). These tests are in addition to full preclinical safety testing of the active ingredient as pure chemicals in laboratory animals, as well as meeting manufacturing criteria controlled by GMP. For these studies, the target species is exposed to the product at various doses above that recommended to elucidate all known side effects, which may then be recorded on the package insert. At present this is the only means of evaluating the side effects that a drug formulation could potentially have. In addition the pharmaceutical industry and veterinarians are legally obliged to report any adverse reaction that results from the use of a veterinary medicine or stock remedy in the aim of improving product safety.

While the necessity of drug regulatory control has often been questioned, incidents in other countries where no control exists have highlighted the dangers of open markets, such as the unscrupulous marketing of fake products to the veterinary communities. In another instances, random sampling has shown deficiencies in not only the quantity but the quality of the active ingredients. More importantly since these fake/counterfeit products are freely marketed at lower prices, they essentially kill the market for ethical good quality products as well as commercial veterinary industry. Therefore drug regulatory control is essential to protect the availability of drugs to the veterinary market as well as the veterinary market itself.
Why should we compound?
- As mentioned above the privilege of compounding allows veterinarians the ability to treat animals with available human medical drugs.
- In addition the process makes it possible to manage wildlife as dart cocktails need to be made up for specifically for the species being managed.
- In small animal practice it can allow for the easier dosing of tiny animal with diluted concentrated solutions that would otherwise not be possible.
- Most importantly it allows for the use of certain medication in animals that are not currently available for use in South Africa.

What Should I be wary of Compounding?
- **Formulation Differences:** As mentioned above drugs are formulated in very specific manner by the drug companies. While in many cases these formulations are designed to control the release of the active ingredient, they are also important in protecting the active ingredient. Therefore if the compounded product lacks a specific inactive ingredient, the clinical effect of the active ingredient is automatically reduced e.g. erythromycin is sold commercially as an enteric coated tablet to protect the molecule from the low gastric pH. By crushing these tablets, the outer coating is damaged, which subsequently leads to a high presystemic elimination.

  Another important concept in pharmacology is the bioavailability of the active ingredient i.e. failure in absorption will automatically result in the failure of the product. In pharmaceutics and pharmacokinetics (study of biopharmaceutics) the interrelation of the formulation and absorption is widely accepted. As such any modification to the formulation could therefore result in decrease bioavailability and inefficacy e.g. the use of fentanyl patches in dogs are not always effective as its release characteristics is specific for human skin.

- **The pH of the formulation.** In pharmaceutical manufacture the specific salt of the active ingredient is selected for its stability in formulation. By using a different salt during compounding, one can alter factors such as formulation pH, ionization, stability and absorption. Even preservatives added to a formulation need to be tested for their influence on the pH e.g. the preservative may chemically neutralize the active ingredient. Another important consideration is the use of product for intramuscular administration. Any changes in the pH can cause severe pain, irritation and or muscle damage on administration.

- **Chemical Contamination:** Since the source of the active ingredient in the formulation is not under strict GMP control, the potential for contaminants to enter into the formulation is always present (It has been speculated that some foreign chemical manufacturing companies intentionally profiteer through the sale of poor quality chemical products). While some of these contaminants can be minor toxins, others are very potent and result in mortality. Unfortunately the degree of contamination of the product cannot be tested, as the current tests can only look for certain chemical i.e. you can’t test for everything.
• **Microbial contamination.** A major concern with any formulation is their potential contaminations with a micro-organism e.g. fungal organism grow remarkably well in drug vials. In addition to the microbial contamination directly, metabolic products like endotoxins are also a major concern. The production standard for the preparation of sterile parenteral drug products which pharmaceutical companies follow is clearly stated in the pharmacopoeias. Therefore if parenteral formulations are to be compounded, veterinary dispensaries or pharmacies must meet these strict requirements. This is important to prevent septic or endotoxic complications in treated patients.

The Vet’s legal responsibilities with regards to compounding
Since compounded products usually do not comply with the strict testing requirements, enforced for registration by South African law, the use of compounded products is controlled in the following manner:

• **The Medicines and Related Substances Control Act (Act 101/1965):** A veterinarian may compound or request a pharmacist to compound (via a valid prescription) any product contained within its schedule, on condition that this is per patient (Patient as defined in the Veterinary Act). More importantly compounded products must have a specified shelf-life of only 30 days i.e. these products expire within 30 days of compounding irrespective of the batch size produced. The Act does not allow or make provisions for veterinarians to stock compounded product on shelf per chance it be required i.e. compounding may only be undertaken after consultation. The stocking of compounded product is the responsibility of only the pharmacist. Most important, all compounded medicines are subject to the rules and regulations that govern the schedule (or highest schedule) in which the chosen active ingredient(s) belongs e.g. compounded butorphenol automatically falls under the control of Schedule 6.

• **The Veterinary and Paraveterinary Professions Act (Act 19 of 1982):** According to this Act, veterinarians may not run an open pharmacy. As such the selling or stocking of these compounded remedy in bulk is illegal. The Act also indicates that scripting is a component of the consultation process, and therefore the owner may not be charged additionally for this service if a consult fee has already been levied. In addition the Act also regulates the extralabel use of medicines. From a recent ruling of the Council, veterinarians may only use an animal product extralabel if the informed owner consent is received and at that on condition that an alternate veterinary product is not already registered for use in the country. Lastly the Act states that the vet must protect public health. Therefore the use of compounded products in animals may not be undertaken without taking cognisance of the consumer safety and food drug residues.

• **The Foodstuffs, Cosmetics and Disinfectants Act. (Act 54 of 1972):** This act protects the consumer from potential residues of veterinary remedies in the human food chain. This act states that no person may use any remedy in a food producing
animal if an adequate withdrawal period has not been set. This therefore implies that the veterinarian must set a new withdrawal period whenever a product is used extra-label or being compounded.

**Practical tips when compounding.**

*Companion Animals*

With the current constraints in companion animal practice, compounding will always be a part of the veterinary profession. Therefore when using drugs in this group of animals, ensure that the owner is informed on the extralabel nature of the product, preferably in writing (notes must always be kept in the patient record). Be aware that you are legally responsible for any negative outcome from the use of the said remedy, even if the remedy is prepared by a pharmacist. Avoid using compounded parenteral formulations as they have a greater chance of causing harm.

*Production Animals*

The use of compounded remedies in production animals is not supported due to food safety issues. Therefore whenever any compounded product is used, an adequately scientifically determined withdrawal must be set by a person experienced in pharmacokinetic extrapolations and interspecies scaling. Alternatively, the veterinarian should enforce a withdrawal period of at least three to six months depending on the nature of the compound in use. This applies equally to the wildlife industry, where the potential exists for trophy kills to end up in the food chain, soon after immobilisation.

**Suggestions for the use of compounded medicines**

- Compounding should not be used as a cheap alternate source of medication.
- Compounding should be used when no alternate/suitable remedy is available.
- Ensure that owners are fully informed when compounded products are being used.
- Compounding should preferably be avoided in production animals. When used, it should be reserved as a last resort and on condition that public safety is ensured i.e. set an adequate withdrawal period.
- Compounded drugs have a legal shelf life of only 30 days.
- Compounding is patient specific and therefore compounding product should not be kept of shelf for routine dispensing.

**References**

1) Department of Health, The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 of 1972
4) Department of Agricultures, The Veterinary and Paraveterinary Professions Act, Act 19 of 1982
6) Papich MG, Drug compounding for veterinary patients. AAPS J. 2005 Sep 22;7(2):E281-7

Continuing Education Questions
1) Compounding as a privilege is controlled by the following act?
   a) The Medicines and Related Substances Control Act, Act 101/65
   b) The Farm foods, fertilizers, agricultural remedies and stock remedies Act, Act 36/47
   c) The Foodstuffs, Cosmetics and Disinfectants Act, Act 54 or 1972.
   d) The Veterinary And Paraveterinary Professions Act, Act 19 of 1982

2) Compounding may be best described as
   a) the use of a medicine extralabel in an animal.
   b) the self-formulation of a drug for use in an animal.
   c) the process of writing a prescription for a pharmacist.
   d) the process of formulating a generic medicine

3) Veterinarians are allowed to compound medicines in South Africa as;
   a) veterinarians are best equipped to decide on the correct treatment for a patient
   b) it prevents pharmaceutical companies from unfairly fixing the prices of medication.
   c) many useful medicines are not marketed in South Africa.
   d) pharmacists do not know how to compound veterinary medicines.

4) The sale of medicines are controlled in the republic as;
   a) it prevents counterfeit medications from being sold.
   b) it gives government a means of restricting the ability of a veterinarian to practice veterinary medicine.
   c) it forces companies to register with the South African Revenue Services.
   d) it allows Department of Health issue of import permits at a predetermined cost.

5) When a compounded medicine is dispensed by a pharmacy,
   a) it is required that the active ingredient be tested safety.
   b) it is required that the formulation is tested for its safety.
   c) it is required that the pharmacy meet the necessary manufacturing requirements.
   d) none of the above.
6) Compounded medicines may be;
   a) stocked on shelf within the dispensary of a veterinary practice.
   b) made up directly by the veterinarian within a veterinary practice.
   c) prescribe for use in an animal for periods exceeding 30 days.
   d) sold over the counter by any person at a veterinary practice as they are non-controlled medicines

7) Veterinarians
   a) may sell compounded products in large quantities for use in production animals.
   b) may charge owners for the process of issuing a prescription.
   c) may sell compounded to owners as a cheap alternate to current registered products.
   d) may only use a compounded product if informed owner consent has been received.

8) Compounded medicines may be dangerous because
   a) the active ingredient is not absorbed
   b) the active ingredient is contaminated
   c) the active ingredient is not safe
   d) the active ingredient is not stable in the formulation

9) When compounding butorphenol,
   a) the product is subject to the rules and regulations governed by Schedule 3
   b) the product is subject to the rules and regulations governed by Schedule 4
   c) the product is subject to the rules and regulations governed by Schedule 5
   d) the product is subject to the rules and regulations governed by Schedule 6

10) The following statement regarding the setting of withdrawal periods for compounded products is incorrect;
    a) veterinarians must always set a withdrawal period.
    b) if a veterinarian is unable to set a withdrawal period, a period of 3 to 6 months is an acceptable alternate.
    c) withdrawal periods need not be set in wildlife.
    d) withdrawal periods are controlled by the Foodstuffs, Cosmetics and Disinfectants Act.

Answers
1. a 6. b
2. b 7. d
3. c 8. b
4. a 9. c
5. d 10. c