



Secundum Artem

*Current & Practical Compounding
Information for the Pharmacist.*

VETERINARY COMPOUNDING

INTRODUCTION

Veterinary compounding is one of the fastest growing specialties in pharmaceutical compounding. It is a practice that is very challenging and rewarding for those compounding pharmacists wanting to spend the time and effort required to learn about individualizing medications for animals (companion, recreational, food and exotic).

Historically, veterinarians have dispensed and compounded their own medications. This has changed in recent years opening up the doors of opportunity for pharmacists to become more actively involved in compounding for veterinary patients.

GUIDELINES FOR VETERINARY COMPOUNDING

Veterinary compounding can be considered, according to the American Veterinary Medical Association, when there are no effective FDA-approved products available, when available dosage forms are inappropriate, when multiple and concurrent disease states are present, when an additive therapeutic effect could be obtained from simultaneous administration of two or more products or to minimize side effects, when economic realities would preclude treatment with the approved product and when compounding would encourage compliance of dosage/therapeutic regimens.

Expanding on the statement concerning inappropriate available dosage forms, compounded dosage forms may be considered when specific products are needed due to patient species, age, size and physiology; also when the safety or individual patient sensitivity or idiosyncrasy. It may also be considered when multiple injections or administrations would be required, when large volumes would be necessary or when the safety of personnel might be compromised in attempting to restrain the animals for dosing.

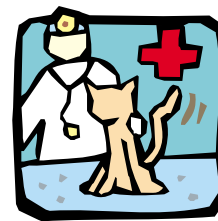
Compounding may also be considered necessary under a number of other situations. For example, when there is a necessity for multiple injections in the absence of a compounded product; also because of rapid changes in the management and disease problems in veterinary medicine; due to the problems associated with the treatment of large numbers of animals with several drugs within a short period of time; cost-prohibitive factors associated with a very large volume of some large-volume parenterals required; and, there is a need for previously prepared antidotes for use in cases of animal poisoning.

REGULATORY AND GUIDELINES

Regulatory and governing documents related to veterinary compounding include the National Association of Boards of Pharmacy Good Compounding Practices, individual state boards of pharmacy regulations and the American Veterinary Medical Association Guidelines for Pharmaceutical Compounding. Most pharmacists are familiar with the NABP and state compounding requirements but may not be familiar with the AVMA Guidelines, which were approved in July 1991 and amended by the AVMA Executive Board in November 1991. They are as follows:

- I. The resulting medicament (veterinary compound) is a restricted product that:
 - A. Must be used only by or on the order of a licensed veterinarian.
 - B. Must be used only within the confines of a valid veterinarian/client/patient relationship and follow the AVMA Guidelines for Supervising Use and Distribution of Veterinary Prescription Drugs.
 - C. May be used or dispensed only for the treatment or prevention of disease or to improve the health and/or welfare of the animal(s).
 - D. May be used only when a need has been established and FDA-approved products are not available or clinically effective.

There is an opportunity for pharmacists becoming more actively involved in compounding for veterinary patients.



A pharmacist must work in close harmony with the veterinarian to develop dosage forms.

II. The veterinarian must use professional judgment consistent with currently acceptable veterinary medical practice in ensuring the safety and efficacy of the medicament including:

- A. The safety for the target animal.
- B. The avoidance of violative residues in meat, milk, or eggs when administered to a food-producing animal.

III. The veterinarian must use professional judgment consistent with proper pharmaceutical and pharmacologic principles when compounding medicaments. The following points should be considered.

- A. The stability of the active ingredients.
- B. The physical and chemical compatibility of the ingredients.
- C. The pharmacodynamic compatibility of the active ingredients.
- D. The active ingredients and diluents must be of known composition and not contaminated with harmful substances or agents.

IV. The prepared medicament must be properly labeled before being dispensed.

- A. When the medicament is administered by the veterinarian or is administered under his or her direct supervision, no label is required.
- B. When the medicament is dispensed according to the veterinarian's order, the product must have a complete, indelible, legible label attached.

A complete label requires the following:

1. Name and address of the attending veterinarian;
2. Date dispensed;
3. Medically active ingredients;
4. Identity of animal(s) to be treated (i.e., species, class, group, or individual animals);
5. Directions for use;
6. Cautionary statements, if needed;
7. Slaughter-withdrawal times and /or milk withholding times, if needed.
8. These requirements are consistent with the AVMA Guidelines, the Pasteurized Milk Ordinance, and the Extra-Label Drug Use Compliance Policy Guide.

Additional information that may be included on a label:

9. Disease conditions to be treated;
10. Expiration date.

V. Compounded medicaments must not be advertised or displayed to the public.

VI. When compounded medicaments are used, appropriate patient records must be maintained.

VII. When compounded medicaments are used in food-producing animals, appropriate drug residue tests, when available and practical, and other procedures for assuring violative residue avoidance should be instituted.

THE MARKET PLACE, FDA AND VETERINARY PRODUCTS

Most drugs that are FDA-approved are generally for certain species, either food producing or for a large target-population. If veterinarian pharmaceutical companies do not perceive a sufficiently large market for a product, they will not seek approval for products. This has left a large vacuum, or a potential market, that can be filled by compounding pharmacists. There are no FDA-approved products for exotic species due to the limited market and there are only limited FDA-approved products for some of the

more common species. Veterinarians need patient-specific products and pharmacists know how to prepare these products; consequently, a team approach has developed to the benefit of the veterinarian, pharmacist and animal patient.

VETERINARY CONSIDERATIONS

Questions that can be asked when considering compounding a specific prescription for a specific animal or animals, include the following. What is the overall goal of the treatment of this animal? Are there any commercially available products that can be used? What are the regulatory concerns? Is this a food or a milk-producing animal? Is there going to be a residue problem? What do we know about the physical and chemical compatibility of these drugs? How about the stability of these drugs before, during and after the compounding process? What about the pharmacokinetics of the active ingredients? Are personnel going to be at risk from handling the drug during compounding or while using the compounded form?

In compounding for humans, we are generally working with patients for which we have a reasonably good understanding and can reasonably predict what should happen when a drug is administered. We also have a relatively defined patient size and weight to work with, even though it does range from infants to adults (about 3 kg to about 115 kg). However, when working with veterinary patients, one may be working with patients as small as a bird or as large as an elephant. Obviously, most dosing regimens do not apply and the pharmacist must work in close harmony with the veterinarian in developing these dosage forms.

Also, it is generally desired, as in humans, to administer most drugs orally. Consequently, there have evolved some suggested flavors for veterinary compounding; these can be modified and extended as the need arises.

Another factor that is involved in compounding for food-producing animals is the requirement concerning drug residues. In these animals, it may be necessary to select products that have a short half-life so they are readily eliminated from the animal prior to market. In other words, when working with food-producing animals, one is concerned not only with the welfare of the animal, but also with public health.

Another area requiring diligence on the part of the pharmacist is in the difference in how certain animals respond to different drugs; they are not uniform. For example, acetaminophen should not be administered to cats due to a deficiency in glucuronyl transferase, required to metabolize the drug, and death may occur. Animals differ in their hydration during sickness with some species maintaining suitable hydration and others not; this alters the drug distribution within their bodies as well as its metabolism and excretion.

The pharmacokinetics of drugs in animals, similar to man, is dependent upon the movement of a drug throughout the body and the effect is related to the concentration that occurs at the site of action. As in man, factors influencing drug concentration at the site of action include the size of the dose, formulation of the drug, route of administration, extent of distribution and plasma protein binding and rate of elimination; factors which may be different from animal to animal. Also, one must consider feeding and digestion differences in animals for products administered orally. For example, the stomach of a horse is seldom empty and the emptying rate of multi stomach animals can be quite variable. Metabolism of drugs differs from animal to animal and excretion rates vary (the urinary pH of herbivores is slightly alkaline but of carnivores is

slightly acidic).

Are there any drug interactions or evidence of reduced efficacy when some drugs are mixed with other drugs or with certain excipients. Each product should be thoroughly investigated. For example, in the presence of bentonite, the following drugs may exhibit reduced efficacy; amprolium, buquinolate, carbadox, decoquinolate, morantel tartrate, nequinolate, oleandomycin, pyrantel tartrate, robenidine hydrochloride, thiabendazole, tilmicosin and tylosin. In these situations, an alternative to bentonite should be used.

ROUTES OF ADMINISTRATION AND DOSAGE FORMS

Factors involved in deciding the route of administration of veterinary formulations include: What is the concentration of drug needed at the site of action? Where is the drug needed in the body? How fast is the action of the drug needed? What should the duration of action of the drug be? Are there any problems associated with this route of administration? How safe is the treatment? What is the cost of the treatment?

Routes of administration for animals include oral, parenteral, implants, intramammary, topical and body cavity. Different dosage forms can be selected for the different routes of administration.

Oral dosage forms generally include solutions (the most readily available form for absorption), emulsions, suspensions, pastes, gels, capsules, tablet, boluses, powders, granules, rumen-retention and feed/water/lick blocks. The rumen-retention and feed/water/lick blocks can be used when long term drug administration is required. The feed/water/lick block dosage forms can be used when treating an entire herd. Most dosage forms for oral use are very similar to those for human use. They often differ, however, in the flavoring used to enhance compliance. The advantage to pastes and gels is they tend to stay in the mouth and do not readily drip out, as compared to a liquid. Pastes and gels often also contain an adhesive ingredient to aid in keeping the product in contact with the oral cavity so it is not easily ejected. Example adhesive ingredients include acacia, alginic acid, bentonite, cellulose, tragacanth, xanthan gum, hydroxypropylmethylcellulose, carbomer, colloidal magnesium aluminum silicate and sodium carboxymethylcellulose have all been used for this purpose. Various flavors that are commonly used for orally administered drugs are listed in Table 1. Common excipients for oral liquid dosage forms include antioxidants, buffering agents, chelating agents, coloring agents, density adjusting agents, flavors, humectants, preservatives, thickeners/suspending agents and wetting agents. Common preservatives, antioxidants, chelating agents and thickeners used in veterinary products are listed in Tables 2, 3, 4 and 5, respectively.

Parenteral dosage forms include intravenous injections, intramuscular injections and subcutaneous injections; prepared as aqueous, aqueous organic and oily solutions, emulsions and suspensions. If a drug is insoluble in water, one can either prepare a suspension or a solution that uses a cosolvent system. Cosolvents that can be used such as alcohol, propylene glycol, polyethylene glycol, dimethylacetamide, dimethylsulfoxide and dimethylformamide. Parenteral products must be sterile and may also contain tonicity adjusting agents, buffers, preservatives, antioxidants and viscosity enhancers. For a longer duration of action, the drug can be placed in an oil vehicle and injected intramuscularly.

Implants include both implantable infusion devices and subdermal implants. Implants are generally not extemporaneously

compounded unless under certain situations.

Intramammary administration includes some precautions that must be considered as well as whether or not the animal is currently lactating. Generally an aqueous vehicle, either solution or gel, is preferred for administration and easy removal, but oil-based vehicles have been used. Oil-based products are very commonly used as antibiotics are more stable in an oil environment than in an aqueous environment. Example oils that are used include corn, sesame, peanut and olive oils. It may be necessary to incorporate an antioxidant in the formulation to prevent rancidity. Intramammary products are generally packaged in single-use devices, such as syringes or tubes.

Topical administration includes solutions, suspensions, emulsions and solids. Generally lotions, liniments, creams and ointments are best for unabraded sites and dusting powders, lotions and aerosols for abraded sites. Topical application methods include creams/ointments, pour-ons/spot-ons/dips (solutions, suspensions, emulsions) and even transdermal patches. If dips are to be prepared, they can be prepared as concentrates that are added to water in the dipping tank. As in topicals for human patients, there is a wide variety of solvents and vehicles that can be used for veterinary compounding.

Body cavity administration includes rectal, vaginal, otic, intranasal and ophthalmic. Rectal and vaginal administration generally involves suppositories and enemas (solutions, suspensions, emulsions and gels). Otic administration generally involves solutions, suspensions, ointments, otic cones and powders. Intranasal administration generally includes solutions (drops/spray/mist) or powders. Ophthalmic preparations generally are sterile aqueous or oily solutions, suspensions, emulsions or ointments. These products should generally be sterile, isotonic and buffered; multidose ophthalmic products should contain a preservative.

STABILITY GUIDELINES FOR VETERINARY PRODUCTS

In general, veterinary products share the same stability guidelines as products for human use; they must be chemically, physically, microbiologically, therapeutically and toxicologically stable. Chemical stability requires that each ingredient retain its chemical integrity and labeled potency, within specified limits. Physical stability requires that the formulation retain its original physical properties, including appearance, palatability, uniformity, dissolution and suspendibility. Microbiological stability relates to sterility or resistance to microbial growth. Antimicrobial agents that are present must retain effectiveness within the specified limits. The pharmacist must continually observe products for evidence of instability. For compounded prescriptions, the USP guidelines state that the following guidelines can be used for beyond-use dating unless stability information is available for a specific drug and preparation. These guidelines (presented here from the USP 23/NF 18) are for nonsterile compounded drug preparations packaged in tight, light-resistant containers and stored at controlled room temperature unless indicated otherwise.

For nonaqueous liquids and solid formulations:

(Where the manufactured drug product is the source of active ingredient)—The beyond-use date is not later than 25% of the time remaining until the product's expiration date or 6 months, whichever is earlier.

(Where a USP or NF substance is the source of the active ingredient)—The beyond-use date is not later than 6 months.

For water-containing formulations (prepared from ingredients in solid form): The beyond-use date is not later than 14 days when stored at cold temperatures.

For all other formulations:

The beyond-use date is not later than the intended duration of therapy or 30 days, whichever is earlier.

Note: These beyond use dates may be exceeded when there is supporting valid scientific stability information that is directly applicable to the specific preparation (i.e., the same drug concentration range, pH, excipients, vehicle, water content, etc.)

Example Formulations for General Purpose Vehicles

ORAL AQUEOUS LIQUID VEHICLE FOR HORSES

(This vehicle is especially good for administering oral sulfonamides to horses)

Xanthan gum	0.5 g
Sodium benzoate	0.2 g
Saccharin sodium	0.5 g
Nutrasweet	0.2 g
Citric acid	0.1 g
Apple Flavor	qs
Purified Water	100 mL

1. Dissolve the sodium benzoate, saccharin sodium, aspartame, citric acid and apple flavor in the purified water.
2. Add the xanthan gum, mix well and allow to hydrate.



ORAL OILY LIQUID VEHICLE FOR HORSES

Peanut butter	10 g
Peanut oil	qs
	100 g

1. Heat the peanut oil to about 40-45°C.
2. Incorporate the peanut butter and mix well.

FLAVORED PASTE GENERAL VEHICLE

Carbopol 934	1.0 - 1.5 g
Triethanolamine	0.23 - 0.35 g
Propylene glycol	qs
Flavor	qs
(Chicken/cheese/beef/liver/apple/etc)	

1. Dissolve the flavor in the propylene glycol.
2. Add the Carbopol 934 and mix well.
3. Add the triethanolamine to the desired viscosity.

Example Injectable Vehicle (Buffering agents and tonicity agents can be adjusted depending upon the active drug to be incorporated)

Potassium phosphate monobasic	200 mg
Potassium phosphate dibasic	240 mg
Methylparaben	100 mg
Sodium metabisulfite	50 mg
Sodium chloride	220 mg
Water for injection	qs
	100 mL

1. Dissolve the powders in the water for injection.
2. Filter through a sterile 0.2 μ filter into sterile containers.
3. Package and label.



Example Formulations for Dogs

MANGE OR RINGWORM OINTMENT FOR DOGS

Rx	Peruvian Balsam	12 g
	Sulfur Ointment	88 g

1. Mix the Peruvian Balsam with the Sulfur Ointment, geometrically.

(Note: Sulfur Ointment contains Sulfur 10 g, Liquid Petrolatum 10 g and White Ointment 80 g; White Ointment contains 5% White Wax in 95% White Petrolatum.)

HUNTING DOG OINTMENT

Rx	Coal tar solution	15 mL
	Lanolin	30 g
	Resorcinol	10 g
	Liquefied phenol	7 mL
	Aquabase™	60 g
	White petrolatum	qs
		454 g

1. Determine the quantity of each ingredient based on the total amount to be prepared.
2. Accurately weigh/measure each of the ingredients.
3. Place the resorcinol on a pill tile.
4. Add the coal tar solution slowly to dissolve the resorcinol.
5. Incorporate this mixture into a small portion of the Aquabase.
6. Add the lanolin and the remaining Aquabase.
7. Incorporate the Liquefied phenol.
8. Incorporate the White petrolatum geometrically and mix well.

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Mortar & Pestle!

YES, I would like to enter the current *Secundum Artem* Mortar & Pestle Drawing.

1. How many prescriptions do you compound per month? _____
2. What powders do you use in your compounding?

_____ Hydrocortisone	_____ Nystatin
_____ Progesterone	_____ Other _____

Name Mr. Ms. _____ Title _____

Pharmacy Name _____

Pharmacy Address _____

City _____ State _____ Zip Code _____

Phone () _____ Fax _____ Email _____

Send in completed BRC today!



TABLE 1**EXAMPLE FLAVORS THAT CAN BE USED FOR VETERINARY MEDICATIONS.**Companion and Recreational Animals

Birds	Grape, molasses, orange, pina coloda, tutti-frutti
Cats	Beef, butterscotch, cheese, chicken, liver, molasses, peanut butter, salmon, sardine, tuna
Dogs	Beef, cheese, chicken, liver, marshmallow, molasses, peanut butter, raspberry, strawberry
Horses	Alfalfa, apple, blue grass, caramel, cherry, clover, forage, molasses

Food Animals

Cattle	Alfalfa, anise, blue grass, clover, forage, maple, meal, molasses
Emu	Watermelon, kiwi, honey dew, cantaloupe, strawberry
Goats	Apple, caramel, molasses
Poultry	Butternut, corn, meal, milk, watermelon
Swine	Anisette, corn, cherry, meal, milk, sarsaparilla, licorice

Exotic and Other Animals

Ferrets	Fish, fruits, molasses
Gerbils	Orange, tutti-frutti
Iguanas	Cantaloupe, kiwi, Mandarin orange, watermelon
Primates	Banana, chocolate, raspberry
Rabbits	Banana creme, celery, lettuce
Some Reptiles	Banana creme, lemon custard

TABLE 2**PRESERVATIVES THAT ARE USED IN VARIOUS VETERINARY PRODUCTS.**

- Benzalkonium chloride
- Benzoic acid
- Butylparaben
- Cetyltrimethylammonium bromide
- Ethanol
- Ethylparaben
- Phenol
- Phenylmercuric acetate
- Potassium sorbate
- Propylene glycol
- Sodium benzoate
- Sodium propionate
- Thiodipropionic acid
- Benzethonium chloride
- Benzyl alcohol
- Calcium sorbate
- Chlorobutanol
- Ethorbic acid
- Methylparaben
- Phenylethyl alcohol
- Phenylmercuric nitrate
- Propionic acid
- Propylparaben
- Sorbic acid
- Sodium sorbate

TABLE 3**ANTIOXIDANTS THAT ARE USED IN VETERINARY PRODUCTS.**

- Ascorbic acid
- Butylated hydroxyanisole
- Calcium ascorbate
- Dilauryl thiodipropionate
- Hydroquinone
- Monothioglycerol
- Propyl gallate
- Potassium metabisulfite
- Sodium ascorbate
- Sodium formaldehyde sulfoxylate
- Sodium thiosulfate
- Thioglycolic acid
- Thiourea
- Ascorbyl palmitate
- Butylated hydroxytoluene
- Cysteine hydrochloride
- Ethoxyquin
- Isoascorbic acid
- Nordihydroguaiaretic acid
- Potassium bisulfite
- Sodium metabisulfite
- Sodium bisulfite
- Sodium sulfite
- Stannous chloride
- Thiosorbitol
- Tocopherols

TABLE 4**CHELATING AGENTS THAT ARE USED IN VETERINARY PRODUCTS.**

- Citric acid
- Gluconic acid
- Sodium ethylenediaminetetraacetate
- Ethylenediaminetetraacetic acid
- Saccharic acid
- Tartaric acid

TABLE 5**THICKENING AGENTS THAT ARE USED IN VETERINARY PRODUCTS**

- Acacia
- Alginic acid
- Carbomer
- Cellulose
- Colloidal silicon dioxide
- Hydrogenated castor oil
- Hydroxypropyl cellulose
- Microcrystalline cellulose
- Polyvinyl alcohol
- Xanthan gum
- Agar
- Bentonite
- Carboxymethylcellulose sodium
- Colloidal magnesium aluminum silicate
- Gelatin
- Hydroxyethyl cellulose
- Methylcellulose
- Polyethylene
- Tragacanth

SUGGESTED READINGS

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To learn more about veterinary physiology, anatomy and therapy, the following sources are available for reference.

Textbook of Veterinary Physiology
James G. Cunningham
W.B. Saunders & Company
July 1997.

PADDOCK'S WEBSITE INFORMATION

For up-to-date compounding formulas, product information and a complete listing of Secundum Artem articles, visit Paddock Laboratories website: www.paddocklabs.com

Textbook of Veterinary Anatomy, 2nd. ed.,
K.M. Dyce
W.B. Saunders & Company
January 1996

Current Veterinary Therapy
Robert W. Kirk and John D. Bonagura
W.B. Saunders & Company



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