

EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists and pharmacy technicians will be able to

- List food items which may be harmful to certain pets
- Identify additives which should not be used in veterinary compounding
- Discover when veterinary compounding is acceptable
- Recognize federal laws pertaining to veterinary compounding
- Investigate labeling requirements for veterinary compounds



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You Asked for It! CE



Considerations in Veterinary Compounding

TARGET AUDIENCE: Pharmacists and pharmacy technicians who compound medications.

ABSTRACT: With an estimated 65.1 million households with dogs and another 46.5 million households with cats in the U.S., veterinary practices are booming with business. Knowing what to feed them and how to keep them well is becoming increasingly important in compounding pharmacies.

FACULTY: Laura Nolan, CPhT, CSPT, Academic Assistant, UConn School of Pharmacy, Storrs, CT

FACULTY DISCLOSURE: Ms. Nolan has no financial relationships with an ineligible company.

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INTRODUCTION

For many people, pets are a major part of everyday life. They become part of their households and are like family, but like children, none of them come with true owner's manuals. Sure, there are many books on the subject, but who do you trust? And who has the time to read all that stuff? What happens if or when they become sick or injured and need medication?

As a somewhat reticent parent of a very large Weimaraner (OK, my husband and daughter bought him without my knowledge), I was forced to learn rather quickly about the ins and outs of pet ownership. Still, he arrived, and we needed to determine what's best for this 99-pound dufus, who amazingly survived eating an entire box of oatmeal raisin cookies. It wasn't pretty, but that story is reserved for an antidote CE.

At the University of Connecticut School of Pharmacy, advanced compounding students are trained in some veterinary compounding, but most pharmacy schools

do not teach it. This is a bit upsetting since people spend millions of dollars on pets every year. An estimated 65.1 million households are home to dogs and another 46.5 million households have cats in the U.S. With pet ownership comes the responsibility of caring for them. The average cost of veterinary care for a dog is \$730 per year, with cats averaging \$253 per year. In 2022, Americans spent \$136.8 billion dollars on their pets.¹

Increasingly, pharmacy staff need to know some basics about companion animals and their health issues. Pet owners can request a paper prescription from the veterinarian and fill it at community pharmacies. The American Veterinary Medical Association (AVMA) incorporated prescription guidelines into their 1991 bylaws. It states that “a veterinarian shall honor a client’s request for a prescription or veterinary feed directive in lieu of dispensing but may charge a fee for this service.”² What do you do when a pet owner brings a prescription to your pharmacy?

People’s perceptions about feeding human food to dogs and cats are surprising. An old wives’ tale, passed from generation to generation, tells us that dogs can eat just about anything, including

bones. Most of us now know that sharp bone shards can penetrate the soft tissues at the back of the throat, they can lodge in the esophagus, or they can pierce the intestines. It is also possible for a piece of bone to lodge in the trachea (windpipe), interfering with a dog’s ability to breathe.³ The controversy still continues today, but no pet owner wants their pet to have broken teeth, mouth injuries, or intestinal blockages if they can avoid it. If cooked bones are out, what else is bad for them? Certain foods create a risk for most pets, so compounders must not use these items as ingredients in their compounds. **Table 1** contains a list of some human foods that should be avoided in pets.

Items like alcohol, tobacco, caffeine, and chocolate make sense. Alcohol and tobacco affect dogs and cats as they do humans, but our pets are much smaller, so it takes significantly less alcohol or tobacco to cause catastrophic events such as breathing problems, vomiting, diarrhea, coma, or even death. Dogs are curious, and a tobacco or marijuana “cigarette” on the ground might be pretty tasty. The average tobacco cigarette contains 10 to 12 milligrams of nicotine. A toxic dose of nicotine for a pet is 0.5 to 1 milligram per pound, and a 4-milligram dose per pound can be

Table 1. Human Foods That Should Not Be Given to Pets⁴

Food Item	Type of Pet	Toxicity/Reasoning
Alcohol	Dogs, cats, chickens, rabbits	Alcohol poisoning
Tobacco	Dogs, cats	Nicotine
Onions, chives, garlic (Allium family)	Dogs, cats, chickens, rabbits	Sulfates, disulfides
Avocado	Dogs, cats, chickens, horses, cows, pet birds	Persin
Salt	Dogs, cats, chickens	Fluid imbalance
Spicy foods	Dogs	G.I. upset
Grapes, raisins	Dogs, cats, rabbits	Kidney failure
Caffeine	Dogs, cats, rabbits	Methylxanthines
Chocolate	Dogs, cats, horses, rabbits	Theobromine and caffeine
Citrus fruits	Cats, chickens	Citric acid, essential oils
Cinnamon	Dogs, cats	Mouth and throat irritant
Nutmeg	Dogs, cats	Myristicin
Macadamia nuts	Dogs, cats	Toxicity unknown
Mushrooms	Dogs, cats	Mycotoxins
Green tomatoes, raw potatoes	Dogs, cats, chickens, horses, rabbits	G.I. upset, bloating, empty calories
Raw bread dough, raw yeast, bread	Dogs, cats, horses, rabbits	G.I. upset, bloating, empty calories
Rhubarb leaves	Chickens, rabbits	Poisonous because they contain oxalic acid
Dairy items, ice cream	Dogs, cats, chickens, horses, rabbits	High sugar, high fat, lactose intolerance. Adult cats become lactose intolerant
Sugar free gum and sugar free candy	Dogs, cats	Xylitol
Seeds and Pits	Dogs, cats, chickens, horses, rabbits	Cyanide
Turkey skin, chicken skin, ham	Dogs, cats, rabbits	High fat content, can cause acute pancreatitis
Marijuana	Dogs, cats, horses, rabbits	Tetrahydrocannabinol (THC)

lethal.⁵ Doing some quick math, consuming as little as three or four cigarettes could be fatal to a 10-pound dog.

Vaping has become extremely popular, which has caused an increase in nicotine poisonings. An average 6 mL, 5% nicotine e-cigarette can contain up to 300 mg of nicotine. Pets can be subjected to nicotine poisoning by secondhand smoke, through spillage on skin, and by drinking the vaping liquid. Consider this: a 40-pound dog would only need to be exposed to a 1 mL dose for it to become poisoned.⁵ Nicotine is not the only toxin in e-cigarettes. They also contain volatile organic compounds, heavy metals (e.g., cadmium, copper, lead, nickel, tin) and they contain propylene glycol. All of these components are harmful to pets.

Those other “cigarettes” can be pretty tasty too. Marijuana use is on the rise in the U.S. since it is now legal in more than 21 states, and for the first time, it has now made its way onto the list of the top 10 items that cause pet poisonings. The two major components of marijuana are cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). CBD is nontoxic to animals, whereas THC is the psychoactive ingredient that is extremely toxic. CBD is widely advertised for human and pet use, but consumers must read labels carefully. Most CBD products are not entirely pure. They contain small amounts of THC.⁶

Although secondhand smoke and consuming raw marijuana leaves can be toxic, the most reported intoxications come from pets eating infused edibles. Edibles like brownies, cookies, or gummies are made with concentrated THC infused oils or THC-infused butter. They tend to be a more significant threat since most edibles also contain chocolate or xylitol.⁷ If pets exhibit any symptoms, they should be taken to a veterinarian. THC poisoning closely mimics the signs of antifreeze poisoning which is fatal and an antidote needs to be given as quickly as possible.^{6,7}

Symptoms of marijuana intoxication can become visible within 30 to 60 minutes after ingestion. Pets may stumble and cross their feet, walking as if they were drunk, they may have enlarged pupils, become lethargic and flinch in reaction to sudden movements. Pets with severe cases of intoxication may vomit, have tremors, shake uncontrollably and in extreme cases become comatose. Roughly 50% of dogs develop urinary incontinence and dribble urine uncontrollably (which might make the drug less popular if this happened in humans).⁷

Some medications contain significant amounts of alcohol. If unsecured, a dog or cat could consume them. Certain formulations of diphenhydramine (Benadryl, Sominex), guaifenesin with codeine (Cheracol Plus), dextromethorphan, guaifenesin, pseudoephedrine combinations (Dimetane, Robitussin, Triaminic, Vicks), hydrocodone and pseudoephedrine combinations (Novahistine), and certain multivitamin liquids (Geritol) contain alcohol. Some remedies can contain up to 25% alcohol, which can harm pets (and children).⁸ Alcohol is sweet tasting to dogs, so they will not stop drinking it until it is all gone.



Caffeine and chocolate ingestion should also be taken seriously. Caffeine contains methylxanthines, which can cause bronchodilatory and stimulatory effects in humans. In animals, they can also cause vomiting, diarrhea, hyperactivity, seizures, and cardiac arrhythmias. Chocolate, derived from the roasted seeds of *Theobroma cacao*, contains methylxanthine, theobromine, and caffeine. The theobromine content in chocolate is three to ten times that of caffeine. Cats do not have taste buds that can detect sweetness, but dogs do have a sweet tooth and love the taste of chocolate. One ounce (28 grams) of chocolate could be a lethal dose in a small dog. Theobromine has a half-life of two to three hours in humans, but it is longer in dogs. The half-life of theobromine in dogs is 17.5 hours.^{9,10} The **SIDEBAR** (next page) provides more information about chocolate toxicity in dogs.

Excess salt (sodium chloride) can cause fluid imbalances which could lead to seizures and spicy foods can cause painful vomiting, diarrhea, or stomach ulcers. Dogs, cats, and even birds are very sensitive to salt, so pet owners and compounders should be aware of common items that contain large amounts of salt. For example, sea water, baking soda, homemade play dough, and driveway deicer all contain high concentrations of salt. Sodium chloride poisonings in dogs are most often caused by pet owners who use salt to induce vomiting after the dog has ingested a different toxin. It is important to consult with a veterinarian or pet helpline before administering any type of antidote.¹²

Even seemingly harmless spices can be harmful. Cinnamon can cause mouth irritations and nutmeg, which contains myristicin, can cause hallucinations in smaller animals. Mushrooms contain mycotoxins which can also cause hallucinations, diarrhea, vomiting, or kidney failure and in extreme cases, liver failure.⁴

Although more toxic to cats than dogs, onions, chives, garlic, and all members of the allium family of herbs contain sulfoxides and disulfides, and an oxidant called n-propyl disulfide. These can cause a fatal anemia, called oxidative hemolysis, which affects dogs, cats, rabbits and chickens. Signs of anemia may take several days to appear.^{4,17,18} If a dog is fed a little garlic once in a while it should not be a problem but avoid giving pets garlic supplements. It was once believed that garlic supplements given to dogs could help to repel fleas and ticks, but this has now been proven to be ineffective.¹³

Other problematic vegetables include green tomatoes, raw potatoes, and avocado. The tomato plant's green parts, its stems and leaves, and raw potatoes contain solanine. Solanine is poisonous, even to humans. It has pesticide-like properties and is part of the plant's natural defenses. Solanine can be found in green potatoes and potato tubers (eyes).¹⁴ It is also found in other members of the nightshade family (e.g., eggplant skin).

Avocado is only slightly dangerous to dogs and cats, but extremely dangerous to birds and large animals such as cows, goats, sheep and horses. The bark, leaves, skin, pits and fruit of the avocado contain persin, which is a fungicidal toxin. Persin is an oil soluble compound that seeps into the fruit from the large seed inside. It is similar in structure to a fatty acid, and is harmless to humans, but toxic to most animals. Symptoms of persin toxicity range from edema and mastitis to respiratory distress and heart failure.^{15,16}

Chickens, which are increasingly popular in back yards, are sensitive to many food items. They should not be fed most human foods, but especially avoid feeding them citrus fruits, uncooked rice and uncooked dried beans, fruit seeds and pits, tomato leaves, green potatoes, and rhubarb.¹⁷ Rhubarb's high oxalic acid content binds to minerals and can form kidney stones. Although high in calcium and phosphorus, certain dried beans are acidic and contain hemagglutinin. Hemagglutinins bind to receptors on red blood cells to initiate viral attachment and infection.

Rabbits, guinea pigs, and most herbivores have similar dietary restrictions. Fruit seeds and pits contain small amounts of cyanide, which can be a concern to smaller animals. Cabbage, cauliflower, other gassy vegetables and iceberg lettuce must be avoided. Iceberg lettuce contains lactucarium. Lactucarium (also called lettuce opium), a milky fluid excreted near the base of the lettuce plant, has sedative properties. Rabbits and other herbivores should stick to darker greens.¹⁸

Factors That Influence Toxicity

Each species of animal reacts to toxins differently due to variations in absorption, metabolism, or elimination. The dose of toxin per body weight is a major concern. Other factors include the animal's age, size, nutritional status, stress level, and overall health. For example, most young animals do not have a fully de-

SIDEBAR: How Much Chocolate is Too Much?^{10,11}

Different cocoa beans and chocolate products contain various amounts of methylxanthines. Compounders and veterinary care providers must consider the dog or cat's weight and the amount of chocolate consumed.

Methylxanthine doses of 15 mg/kg (7.5 mg per pound) or less should not harm a dog. This is equivalent to one square of dark chocolate for a 3 kg (6 lb.) dog or seven squares of chocolate for a 15 kg (33lb.) dog. One square of chocolate is approximately 6 grams (0.21 oz). This formula calculates the dose consumed:

- Theobromine dose= concentration in type of chocolate x amount eaten/weight
- Caffeine dose = concentration in type of chocolate x amount eaten/weight
- Theobromine + caffeine = Total methylxanthines

The caffeine and theobromine amounts in the specific type of chocolate may be on the label, and the [Table](#) below provides some information about common products. However, in emergencies, healthcare providers can use calculators on the Internet that performs this calculation quickly and efficiently. This is not to say that cats never get into chocolate and get sick. There are also cat chocolate toxicity calculators online in case of emergency.

Product	Methylxanthines per 1 gram	mg methylxanthines /ounce
Dry cocoa powder	28.5 mg	800 mg
Unsweetened bakers chocolate	16 mg	450 mg
Milk chocolate bar	2.3 mg	64 mg
Dark chocolate bar	5.7 mg	150-160 mg
Cocoa bean hulls (mulch)	9.1 mg	225 mg
White chocolate	Negligible	

veloped system of metabolism, which may cause a toxin to remain in their system longer, causing more harm. Horses, rabbits, and small rodents do not have the ability to vomit, which means that they may be poisoned at a lower dose.¹⁹

One must also consider the chemical nature of a food, drug or poison that is consumed. If the drug or toxin dissolves in water easily, it will spread throughout the body easier. If there are substances added to an active ingredient, such as a binding agent or outer coating, or if it is a sustained release product, it will affect absorption.¹⁹ Overall, pharmacists should become familiar with species specific toxins and the factors that affect the risk of toxic-

ity. Animals absorb, distribute, metabolize, and eliminate medications and toxins differently from humans, and the interspecies differences are also notable. See the **SIDEBAR** for a list of the top ten toxic items.

Evolution has influenced species-specific diets. Dogs have evolved to become opportunistic gorgers, while cats are very picky. A dog will eat every bit of chocolate once he starts, which is the reason why dog poisonings are more common. Cat poisonings are less common and are usually the result of intentional harm by human beings.

Pause and Ponder: Have you tried to give a dog a tablet or capsule? Did you wrap it in some meat or cheese? How did you get a cat to take his dose?

When to Compound

Pharmacists should consider compounding veterinary products under three conditions:

1. **When a commercial product is unavailable.** This could be due to drug recalls, drug shortages, or because a commercial product has yet to be developed. In some cases, rapid changes in disease state management create an urgent need for medication.
2. **When an approved drug needs to be modified.** This would include an increase or decrease in dosage due to a lack of appropriate dosage size, or a lack of formulation for a desired route, for example, making a dilution, adding flavoring, or changing the form of the drug. A popular compounding task is changing a tablet into a suspension.
3. **When the likelihood of nonadherence is high.** Owners' adherence is greater when they can administer one combination product instead of two or three. For example, combining two injectable vaccines or allergy medications into one syringe for ease of use would be helpful to the pet owner. Of course, it is also more beneficial to the animal, since it will minimize harm and stress, which will lead to a better prognosis. Our students have recently formulated a compound of ketoconazole, gentamicin sulfate, and mometasone furoate all in one for a dog with an external ear bacterial yeast infection.

Dogs and cats can be very particular, and their sense of smell will give that medication away every time. This means that compounding must be creative. The most popular forms of medications for veterinary consideration include capsules, transdermal medications, flavored liquids, tablets, chews, or treats. Oral formulations can be difficult to give, but devices such as droppers, mechanical pill injectors, oral syringes, and oral pastes and gels can mask medications. Pill pockets—soft, flexible treats—can be molded around a tablet or capsule. Medicated oral pastes and gels, when placed on a cat's paw, are an ingenious way for the cat to lick his medicine up. Compounders make a variety of prod-

SIDEBAR: ASPCA: The Official Top 10 Toxins of 2022²⁰

Each year, the Animal Poison Control Center of America (ASPCA) compiles a yearly list of toxic items. They received 335,136 pet poisoning calls in 2022 and have tabulated the results as follows:

1. Over the Counter Medications. Ibuprofen and acetaminophen are the most common.
2. Food items. Protein bars, xylitol, grapes and raisins top the list.
3. Human prescription medications
4. Chocolate. ASPCA received approximately five calls per hour regarding chocolate.
5. Plants
6. Household chemicals. Disinfecting wipes top the list.
7. Veterinary products
8. Rodenticides
9. Insecticides. Ant baits are an example.
10. Recreational drugs. Edible THC products are the most common.

ucts from hairball pastes and pectin gels, used for diarrhea, to dental licks and probiotic powders which are placed on cats' fur.

Human compounding caters to the customer, and the same is true for pets. Tuna or salmon flavoring attracts cats; beef or chicken flavoring may fool dogs; and birds love seeds. Other ingredients can be rather generic. Compounders can choose from a myriad of thickeners, sweeteners, and preservatives. Choosing the correct excipient could be crucial.

Pause and Ponder: Take another look at the list of forbidden foods. Which items on your pharmacy compounding shelf could be harmful to pets?

Ingredients for veterinary compounding

In human compounding we tend to lean toward avocado or grapeseed oil to soothe and treat the skin, which are lighter than other oils. We use alcohol, propylene glycol, polysorbate 80 (Tween 80), and essential oils in compounds and peanut butter quite often for dog treats. These may not be the best choices in some veterinary situations. Let's look at what is safe and what should not be used for pets.

Sweeteners

Sugar substitutes are game changers for people who have diabetes or are on low calorie diets. Xylitol is a current human favorite, occurring naturally in small amounts in berries, cauliflower, corn, mushrooms, oats, plums, and pumpkins. In industrial production, the purest form is extracted from raw biomass materials such as hard and soft wood, and especially from the birch tree. More economical processing uses hydrolyzed, purified agricultural corn, wheat, and rice waste. Economists expect xylitol production to become a \$1.4 billion industry by 2025.²¹ Why the in-

crease in popularity? Xylitol contains two-thirds of the calories of sucrose and has a mild increased saliva effect. Unfortunately, xylitol is extremely toxic to dogs.

When dogs consume xylitol, it is quickly released into the bloodstream, causing an immediate and potent release of insulin from the pancreas. This leads to severe hypoglycemia, with onset that can occur anywhere from 10 to 60 minutes after ingestion. Without treatment, the dog may develop liver failure, have seizures, or become comatose.²²

Products that contain xylitol are ubiquitous. It's found in foods such as barbeque sauce, candy, gum, jam, ketchup, low calorie maple syrup, and peanut butter (meaning that compounders who use peanut butter need to check labels carefully; xylitol may be listed as 1,4-anhydro-d-xylitol, anhydroxylitol, birch bark extract, birch sugar, D-xylitol, Xylite, xylitylglucoside, or zylatol). In fact, sugar-free gum is the most common source of xylitol poisoning in dogs. For example, one piece of gum or one breath mint can be fatal to a 10-pound dog. The Pet Poison Helpline responded to 5,846 xylitol poisoning cases in 2020.²²

Xylitol can also be found in many pharmaceuticals and personal care products: cough syrup, deodorant, digestive aids, gummy vitamins, laxatives, mouthwash, nasal sprays, shampoo, skin care products, sleep supplements, toothpaste, and especially orally dissolving tablets. Small traces of xylitol can even be found in prescription medications.²² Gabapentin tablets and capsules do not contain xylitol, but gabapentin oral solution contains xylitol. The **SIDEBAR** discusses one xylitol poisoning case.

Many other sugar substitutes are considered safe to use in veterinary compounding. Erythritol, a sugar used mainly in keto desserts and baked goods, is safe in small amounts. Stevia and aspartame are also considered safe to use, although pets may experience stomach aches or slight diarrhea. Saccharin (Sweet-n-Low), sucralose (Splenda), or monk fruit, a newer sweetener, are all considered safe in pets.²⁴ Dogs have more of a sweet tooth than cats, but in general, sweeteners should be kept to a minimum.

Flavors

Using an optimal flavor profile helps mask the active ingredient's taste and will promote animal adherence. Compounders should use only flavorings that are intended for compounding use. They shouldn't use meat-flavored bouillon cubes or bouillon powders for compounding since they contain high amounts of salt, onion powder, and other harmful spices. **Table 2** (next page) lists common flavorings and the species that find them enjoyable.

Preservatives and Additives

The Food and Drug Administration (FDA) maintains a list of additives generally recognized as safe (GRAS) for use in pet foods. Manufacturers must submit food additives used in their pet foods for FDA review, which if approved, are added to the GRAS list.²⁶

SIDEBAR: POOR MIMI²³

In 2020, Mimi, a pet poodle passed away after receiving gabapentin. The veterinarian prescribed gabapentin oral solution, for ease of use and medication adherence for Mimi's seizures. The owner administered the dose and Mimi's seizures increased, so the owner called the veterinarian, who increased the dose of medication to be given. Within 24 hours Mimi was gone.

How could this happen?

Many veterinarians are unfamiliar with the added ingredients in human formulations. Also, drug manufacturers may change sweeteners without notice. A retail pharmacist filled her prescription for gabapentin oral solution with the commercially available product, which contained xylitol. When the dogs owners went to the pharmacy to investigate, they found several factors which caused the problem.

- They were told that the pharmacist did not know that the solution contained xylitol and he was also unaware that xylitol was harmful to dogs.
- The pharmacy had no drug utilization review processes in place for veterinary drugs.
- The existing built-in computer software was not programmed to issue alerts for xylitol or other veterinary toxins.
- The pharmacy did not have a veterinary drug reference book, for example, *Plumbs Veterinary Medicine*, or a veterinary drug formulary. Unfortunately, the majority of state boards of pharmacy do not require pharmacies to carry a veterinary drug reference book.

Pharmacists and pharmacy technicians need to be aware of additives in human drug formulations that can be harmful to pets. Mimi's death could have been avoided.

Still, many excipients should not be used for veterinary compounding^{27,28,31}

- Butylated hydroxyanisole (BHA)
- Butylated hydroxytoluene (BHT)
- Ethoxyquin
- Propylene glycol
- Polysorbate 80 (Tween 80)

BHA and BHT are preservatives that are added to oils and rendered fats in certain pet foods and treats. They have been found to be carcinogens and can cause liver and kidney damage in rats, but the FDA has cleared them for use in small amounts in pet foods and treats. Ethoxyquin, a preservative, is used as a hardening agent. It is also used in pesticides and

Table 2. Common Flavorings for Pets²⁵

Animal	Flavor	Reasoning
Birds	Banana, grape, orange, raspberry, tangerine, tutti-fruitti, pina colada	Birds prefer sweet and fruity flavors
Dogs	Bacon, beef, liver, chicken, turkey, cheese, peanut butter, molasses, caramel, anise, marshmallow, raspberry, strawberry, honey	Dogs prefer meats and sweets
Cats	Fish, liver, tuna, cod liver oil, sardines, mackerel, salmon, beef, chicken, cheese, bacon, molasses, peanut butter, butterscotch, marshmallow	Cats do not like very much sweetness but hate bitterness
Gerbil	Banana cream, orange, peach, tangerine, tutti-fruitti	Gerbils like sweet and fruity flavors
Iguana	Banana, cantaloupe, kiwi, orange, tangerine, watermelon, other melons	Iguanas and most reptiles rely on sense of smell more than taste, so it must smell good
Rabbits	Banana cream, carrot, celery, lettuce, parsley, pineapple, vanilla, butter-nut	Find their favorite vegetable/fruit and use it
Poultry	Cantaloupe, corn, meal, milk, vanilla, butternut, watermelon	Research is ongoing to determine the sense of taste in chickens.

rubber and is illegal for human use, yet the FDA has ruled the additive “may be safely used in animal feeds” when used according to regulations.²⁷ Which is the best preservative to use? The answer is to stick to more natural preservatives. Vitamin C and E are great choices, as are lemon, except for use in cats and chickens, and honey. Honey is packed with vitamins A, B, C, D, E, and K and also contains potassium, calcium, magnesium, copper, and antioxidants. Giving a pet a small amount of honey can even help to build immunity from some allergens, such as pollen.²⁹

Propylene glycol is a controversial excipient used as a humectant, or moisturizing agent, in many pharmaceutical formulations. Propylene glycol is derived from ethylene glycol, which is antifreeze’s main component. Small amounts may be used in dog formulations, but it is extremely toxic to cats. Extended exposure to propylene glycol over several years has been shown to cause seizures and possible blood disorders in both dogs and cats.²⁸ Cats may develop Heinz body hemolytic anemia, which can lead to death.

Cats and dogs are also extremely reactive to essential oils. Popular essential oils (e.g., eucalyptus oil, peppermint oil, tea tree oil) can be found in some natural flea repellents, perfumes, and aromatherapy products. These are safe to use in humans and can be found in many topical preparations; using these oils in topical preparations for dogs or especially cats (since they are continual groomers), can be harmful. Signs of toxicity are lethargy, depression, ataxia, tremors, seizures, or death.³⁰

Polysorbate 80 (Tween 80) is a surfactant used in soaps and as a lubricant in eye drops. It is also used as an excipient quite often to stabilize aqueous formulations of lipophilic drugs for vaccines and for parenteral administration. Many Chinese herbal injectable medications contain high amounts of polysorbate 80. When dogs are given intravenous (IV) medications that contain high levels of polysorbate 80, for example vitamin K, it causes systemic histamine release, which causes allergic reactions and tachycardia and may lead to an anaphylactic reaction.³¹

SIDEBAR: When to Call a Professional

When should pet owners or concerned pharmacy staff call a professional for a suspected pet poisoning? The sooner the better. The first call should be to the pet’s veterinarian, but national hotlines are also available for emergencies 24/7 for a fee.

- ASPCA Animal Poison Control
<https://www.aspc.org/pet-care/animal-poison-control>
888-426-4435
Free access to website
\$95.00 fee for hotline service.
*90% of the fee is covered with ASPCA insurance
- Pet Poison Helpline
<http://www.petpoisonhelpline.com>
855-746-7661

Corn syrup is a cheap humectant, sweetener, and flavoring agent all-in-one, but it can be addictive to dogs and can increase blood sugar significantly. A vegetable-based glycerin, such as coconut glycerin is a better choice.³²

Food dyes and colorants should be used sparingly when compounding. Blue dye #2, red #40, yellow #5 and #6 can cause hypersensitivity or allergic reactions in some pets. Also, caramel color 4-methylimidazole (4-MIE) is under investigation as a possible carcinogen in pets.³² In actuality, pets do not care about the color of the compound. Artificial coloring only appeals to the pet owner.

General Recommendations for Compounding

Under the Federal Food, Drug, and Cosmetic Act (FD&C Act), the FDA permits compounding of animal drugs when the source of the active ingredient is a finished FDA-approved drug, and not a bulk drug substance (BDS), unless certain exceptions, described below, are followed. A “bulk drug substance” is a substance used to make a drug that becomes an active ingredient in the

drug's finished dosage form.³³ Most pharmacists would recognize that as an active pharmaceutical ingredient (API).

A commercially available drug may not always be available or appropriate for veterinary use. For example, an FDA-approved drug may have excipients or preservatives that are unsuitable for pets, the dose may be too large, or the flavoring may be unacceptable. In this case, the FDA has acknowledged the need for certain bulk drug substances. On April 14, 2022, the FDA released the Guidance for Industry (GFI #256), entitled "Compounding Animal Drugs from Bulk Drug Substances" which became effective in April 2023. The FDA has also created approved BDS lists for use in veterinary preparations.³⁵ Separate BDS lists exist for non-food producing animals, for food producing animals, for veterinary office stock drugs, and certain wildlife species.³⁶ GFI #256 allows pharmacies to purchase and use bulk drug substances from FDA-registered suppliers if a certificate of analysis (COA) is included with the compounding record. The FDA also requires compounders to report any adverse reactions to the FDA within 15 days. Veterinarians must also provide more patient specific detailed clinical information explaining why a pet cannot use an FDA approved manufactured product.

The FDA has composed a check list for pharmacists regarding veterinary compounding.³⁴

1. Confirm whether patient(s) is a nonfood-producing animal or a food-producing animal. Make sure that chicken is just a pet! Food-production animals (cattle, chickens, etc.) have an additional set of rules (not discussed here). Check the FDA guidelines for more information.³³

2. Follow all state laws and regulations that apply to compounding animal drugs. Compounders need to check their state regulations. It appears that most states tend to merely restate FDA animal compounding guidance.

3. Meet USP standards and FD&C Act requirements. Use FDA-approved drugs or FDA-approved BDS, follow USP guidelines and monographs, if they exist, and follow FD&C act requirements.

4. Include all labeling information. See below.

5. Dispense the compounded drug(s) to the patient's owner or caretaker or the veterinarian who prescribed or ordered it. A valid veterinarian-client relationship must exist, and a veterinarian must provide a valid prescription.

6. Report adverse events and product defects associated with the compounded drug to the FDA on Form FDA 1932a.

7. Consider other FDA-approved options first. Check to see if alternative options are available. Compounding is permitted if the active ingredient is a different salt, ester, or other derivative.



8. Determine if you are compounding a copy of an FDA-approved product. If the exact form of medication is commercially available, it cannot be compounded.

9. Obtain a medical rationale and retain it in your records if a copy is needed. The rationale for the compound must be documented on the prescription.

Other considerations include determining the physical and chemical compatibility of the drugs, the drugs' solubility and stability, and the active ingredients' pharmacodynamics.

Labeling

In addition to including the client's name on the label, the American Veterinary Medical Association (AVMA) recommends veterinarians and compounders in veterinary offices convey the following information to animal owners when prescribing all compounded preparations³⁷:

- Name, address, and telephone number of veterinarian
- Identification of animal(s) treated, species, and number of animals treated, when possible
- Date of treatment, prescribing, or dispensing of drug
- Name, active ingredient, and quantity of the drug (or drug preparation) to be prescribed or dispensed
- Drug strength (if more than one strength available)
- Dosage and duration
- Route of administration
- Number of refills
- Cautionary statements, as needed
- Beyond-use date (BUD)
- Slaughter withdrawal and/or milk withholding times, if applicable

Per FDA regulations, pharmacies must include the following on the compounded drug's labeling: name and strength or concentration of drug; species and name or identifier of patient(s); name, address, and contact information for the compounding pharmacy and name of the prescribing veterinarian; a beyond use date; the withdrawal time as determined by the prescribing veterinarian; and the following statements must be included³³:

♣ "Report suspected adverse reactions to the pharmacist who compounded the drug and to FDA using online Form FDA 1932a."

♣ "This is a compounded drug. Not an FDA approved or indexed drug."

♣ "Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian."

CONCLUSION

On June 10, 2021, the FDA finalized Guidance for Industry (GFI) #263, (not to be confused with GFI #256 which was mentioned

previously) requesting that participating animal drug companies voluntarily transition certain antimicrobials from over-the-counter availability to veterinary prescription within two years. The aim of this guidance is to decrease antibiotic resistance in animals, and the target date to introduce new prescription labels onto the market was June 11, 2023.³⁸ These include well known antibiotics such as erythromycin, gentamicin, penicillin, sulfamethoxazole, and tetracycline. This FDA requirement is now in effect for food-production animals and pets, and it may be one reason why many pharmacies have seen an increase in pet prescriptions. Another reason may be that more pet owners trust their local pharmacy to prepare the correct formula for their furry family members.

The field of veterinary medicine is expanding seemingly daily, and it is a field where compounding pharmacies can be instrumental. Veterinary compounding has its challenges, but when collaborating with a veterinarian, the compounder can impart professional judgment to ensure that the compound is safe, effective, and therapeutic. That's a rewarding practice in the end.

Figure 1. Safety and Counseling Related to Veterinary Compounding

Best

- 1 **Be COMMUNITY CHAMPIONS** and whenever possible, advocate for good practices regarding our furry friends—work with local vets and rescues
- 2 **Partner with a veterinarian** so you will know what's being prescribed in your area, and you can be an information source
- 3 **Remember that pets are family members**, and their owners need empathy and compassion as they deal with health issues in their companion animals

Better

- 1 **Remembers that different states have different laws**; keep current on compounding laws!!!
- 2 **Report adverse events to the FDA** through the United States Food and Drug Administration Adverse Event Reporting System (FAERS)
- 3 **Anticipate owners' concerns** about administration and get creative!!!

Good

- 1 **Be familiar with the USP guidelines** and how they apply to veterinary practice
- 2 **Keep a good selection of veterinary references** and don't forget Plumbs!
- 3 **Understand that every pet is an individual** with different needs, JUST LIKE PEOPLE!

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