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WHAT YOU NEED TO KNOW ABOUT COMPOUNDED DRUGS

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INTRODUCTION
Compounding has been an important part of veterinary practice for many years because it has been necessary in the course of routine practice. However, there are restrictions and interactions that should be recognized. Compounding pharmacies have been affected by a new FDA guideline (CPG) issued in July 2003 that prohibits compounding from bulk substances, and the compounding must not constitute manufacture of a new animal drug. Drug compounding on a case-by-case basis is allowed under the CPG. However, veterinarians and pharmacists must be aware of potential incompatibilities and practices that may interfere with the drug’s stability, purity, and/or potency.

CURRENT REGULATIONS ON COMPOUNDED VETERINARY DRUGS
Historically, veterinarians have been known for preparing concoctions, mixtures, and remedies for their patients because there were few approved veterinary formulations on the market. Now, however, there are more available drugs for use in animals, and scientists have acquired a better understanding of factors influencing the risks of drug instability as well as the incompatibility of certain mixtures. Concerns regarding the widespread practice of product compounding have been raised with respect to drug stability, purity, and potency.

Compounding is the alteration of the original drug dosage form for the purposes of ease of administration or because the original dosage form is unsuitable for the purpose intended. According to the United States Pharmacopeia (USP) (1), compounding involves the preparation, mixing, assembling, packaging, and labeling of a drug or device in accordance with a licensed practitioner’s prescription. From the USP chapter on pharmacy compounding, “compounding is an integral part of pharmacy practice and is essential to the provision of health care” (1). Compounding does not include the preparation of a dosage form by reconstitution or mixing if conducted in accordance with FDA-approved manufacturer’s instructions on an approved human or veterinary product label.

The FDA permits compounding on a case-by-case basis and on the order of a veterinarian when there is a need for an appropriate size oral dosage form to produce a more palatable oral drug, to produce a more dilute formulation for a small animal or exotic animal patient, or when it is necessary to administer analgesics for ease of administration. These are expected practices and will not be subject to regulatory action according to the most recent CPG.

The new CPG, published in July 2003, replaces an earlier CPG (2) and is specifically intended to clarify the regulations on compounding from unapproved or bulk drugs. This CPG is available from the FDA, or on the internet (http://www.fda.gov/ora/compliance_ref/cpg/default.htm or http://www.fda.gov/OHRMS/DOCKETS/98fr/03d-0290-gd10001.pdf).

“Bulk drugs” are defined as active ingredients used in the manufacture of finished dosage forms. Compounding from bulk drugs or from unapproved drug substances is not allowed, with the exception of those few compounds provided on a list that will not ordinarily be subject to regulatory action (Appendix A in the CPG). Compounding of these latter compounds may not be subject to regulatory action in instances where the health of the animal is at risk and when no other remedies are available. The list includes antidotes such as methylene blue, or sodium nitrite. A complete list of these bulk compounds is listed in the FDA document cited earlier (3).

Large scale compounding from bulk drugs has been practiced by some pharmacies importing large quantities of raw chemicals. The FDA has seized compounded products from bulk drugs and has issued warnings to pharmacies when there have been regulatory violations (4). Nevertheless, this practice continues to occur, and products are still advertised in plain sight at national trade shows and on the internet without penalty. In reaction to this situation, some organizations have taken steps to discourage illegal compounding. The Journal of the American Veterinary Medical Association recently adopted an editorial policy in which it would not publish papers in which illegal compounded drugs are used in a research study. On the other hand, the International Academy of Compounding Pharmacists (IACP) has expressed concerns about the current CPG (http://www.iacprx.org/vet.html). In a letter to the FDA on September 16, 2003, the IACP called for a withdrawal of the CPG. They have argued that there is a need to compound veterinary medications from bulk ingredients and if this is restricted, “many animals will die, go untreated, or suffer needlessly”. In a related development, on September 27, 2004, pharmacies from several states filed a law suit against the FDA claiming the agency is illegally enforcing the current regulations on compounding.

THE NEED FOR COMPOUNDED DRUGS IN VETERINARY MEDICINE
Palatability, ease of administration, and dispensing factors are among the considerations used when formulating drugs for animals. Drugs intended specifically for animals and registered by the FDA are designed with great care. Pastes and dosage syringes are available for some drugs used in horses. Flavored tablets are often available for dogs to ease administration by pet owners. To prevent parasite infestations, transdermal medications are available for dogs and cats to avoid the necessity of frequent administration to a pet that may be difficult to medicate. One of the largest costs to pharmaceutical companies when developing new drug products is the determination of an appropriate formulation. When companies spend literally millions of dollars “getting the formulation right” in terms of stability, solubility, and palatability, it is risky to expect that new drug formulations compounded in a pharmacy will have the same assurance of stability, purity, and potency.

Sometimes, compounding is a necessity. Despite advances in new drugs available for animals, many unmet needs still remain. Therefore, many drugs are crossed over from one animal species to another, or are human drugs administered to animals. According to a 1999 survey (5), the top ten drugs that are compounded for veterinary medicine are: potassium bromide, metronidazole suspension, methimazole oral liquid, diethylstilbestrol capsules, cyclosporine ophthalmic solution, prednisone oral liquid, amitriptyline oral liquid, chloramphenicol oral suspension, and protamine zinc insulin. Much of the compounding cited in the
article consisted of mixing drugs with various foods and flavorings in an effort to ease product administration to hard-to-medicate pets or exotic species.

**POTENTIAL PROBLEMS CAUSED BY COMPOUNDED FORMULATIONS**

Some compounded drug formulations can present problems if the safety and potency of the compounded product have not been considered. Tablets that must be crushed or broken to deliver a smaller dose size to dogs or cats may be unpalatable for oral use in animals. When drugs are administered to cats, either a portion of a tablet must be given, or the drug is reformulated into a capsule. Because ill cats are usually anorectic and because cats generally do not drink water frequently, solid dose forms have become trapped in the esophagus of cats. The latter problem was documented in two studies in which capsules were orally administered to cats (6, 7). When capsules containing barium sulfate were followed radiographically, they became entrapped in the midcervical region of the esophagus 53% of the time. These capsules pass into the stomach when followed by food. In another study, a dry capsule given to cats was retained in the esophagus for greater than 300 seconds 63% of the time. (Recordings were not made later than 300 seconds.) Wet capsules passed 97% of the time at 30 seconds and 100% of the time thereafter. The location of the entrapment of capsules is particularly disturbing because some medications given to cats such as doxycycline, tetracycline, propranolol, iron supplements, and bromide are known to cause esophageal lesions in experimental cats (8, 9).

Because many drugs are not in a form that is ideal for the species being treated (e.g., cats, exotic animals, pet birds), the tablets have been crushed, capsules reformulated, and solutions altered to make a more convenient and palatable oral dosage form. However, when protective coatings are disrupted and vehicles are altered, the stability of the product may be compromised. In some instances, the only change is a slight alteration of pH. But, according to the USP-NF (10), "improper pH ranks with exposure to elevated temperature as a factor most likely to cause a clinically significant loss of drug. A drug solution or suspension may be stable for days, weeks, or even years in its original formulation, but when mixed with another liquid that changes the pH, it degrades in minutes or days. It is possible that a pH change of only one unit could decrease drug stability by a factor of ten or greater." Addition of a water-based solution to a product to create a liquid solution or a suspension results in the hydrolysis of certain compounds (e.g., β-lactams, esters). Some drugs undergo epimerization (steric rearrangement) when exposed to a pH range higher than what is optimum for the drug (for example this occurs to tetracycline when exposed to a pH higher than 3). Other drugs are oxidized, a reaction catalyzed by exposure to a high pH, rendering the drug inactive. Drugs most likely to be subject to oxidation are those with a hydroxy group bonded to an aromatic ring structure. Oxidation may occur from exposure to light and oxygen during reformulation and mixing.

Veterinarians and pharmacists are obligated to be cognizant of the potential for interactions and interferences with stability. Oxidation is often visible through a color change (e.g., color change to pink or amber). Loss of solubility may be observed through precipitation. Some drugs are prone to hydrolysis from moisture. A rule-of-thumb for veterinarians is that if a drug is packaged in blister packs or in moisture proof barrier, it is probably subject to loss of stability and potency if mixed with aqueous vehicles. If compounded formulations of solid dose forms show cracking, "caking", or swelling, the formulation has probably acquired moisture and may have lost potency. Another rule-of-thumb is that if the original packaging of a drug is in a light-protected or amber container, it is probably prone to inactivation by light. Vitamins, cardiovascular drugs, and phenothiazines are labile to oxidation from light during compounding. Also, as a general rule, if an antibiotic is available in a powder that must be reconstituted in a vial or in an oral dispensing bottle prior to administration, it should not be mixed with other drugs.

**EXAMPLES OF PROBLEMS**

There are very few published studies in which drugs for veterinary patients have been tested for stability under the conditions used during compounding. In a commercial formulation, the active ingredients and the excipients added to drug formulations are tested and must meet FDA-approved specifications to ensure the stability of the drug and to insure uniformity in product in vivo performance. However, the addition of other chemicals, flavorings, and vehicles, or by interfering with protective coatings of tablets, a compounder may interfere with the stability of the drug, decreasing its potency, compromise its oral absorption, and consequently reduce its efficacy. There are published recipes in compounding journals, magazines, and handbooks, but few of these formulations have been tested for their stability, potency, and purity. Veterinarians have an obligation to question their compounding pharmacist about the stability and potency of formulations he/she prepares for their patients and to insist on some valid documentation. When veterinarians compound formulations in their own practices, they should be cognizant of the potential interactions and alterations that may compromise product performance.

There are a few published examples in which drug stability and efficacy has been compromised through compounding. For example, when omeprazole was compounded for oral use in horses, it was not as effective for treating gastric ulcers as the commercial formulation registered for horses (Gastroguard) (11). Systemic absorption of the compounded formulation was lower than that of the proprietary product. Omeprazole is known for its instability, a problem minimized in the original formulation intended for use in horses or people.

Fluoroquinolone antibiotics are frequently modified for administration to exotic animals and horses. Our laboratory has evaluated the compatibility of enrofloxacin and orbifloxacin with flavorings, vehicles, and other ingredients. We found that, with few exceptions, this class of drugs is compatible with most mixtures, and remarkably stable. A notable exception is the chelation of enrofloxacin with aluminum-containing products (e.g., antacids, sucralfate), resulting in a significant portion of the medication becoming unavailable for absorption. We also documented that certain mixtures and flavorings may be incompatible with fluoroquinolones if they contain metal ions that are known to cause chelation. For example, we found that if crushed orbifloxacin tablets are mixed with Lixotinic, a vitamin and mineral supplement that is sometimes used as a flavored vehicle for oral drug administration, orbifloxacin bioavailability was reduced to half that seen with the original formulation. The decrease in drug bioavailability was attributable to the high levels of iron contained within this flavorant (2.5 mg/mL). Other flavorings, and vehicles (for example, corn syrup,
molasses, fish sauce, and Syrpalta) had no affect on orbifloxacin absorption.

Antifungal drugs also are subject to instability. Itraconazole is frequently compounded from bulk drugs or the proprietary capsules. However, during compounding, inactivation may occur. Itraconazole may absorb to plastic and glassware, decreasing product drug concentrations. Recently in our laboratory, a clinician requested an assay of a 100 mg capsule of itraconazole that was formulated by a compounding pharmacist. We found that the concentrations of itraconazole or the metabolite hydroxyitraconazole were undetectable from the compounded capsule.

Aminoglycoside antibiotics (gentamicin, tobramycin, and kanamycin) are inactivated when admixed with other antibiotics, particularly beta-lactams. This interaction is greatest with carbencillin, followed by ticarcillin, penicillin G, and ampicillin. Loss of potency by as much as 50% can occur within 4 to 6 hours. This interaction is a potential problem when antibiotic mixtures are prepared and dispensed for use several hours later. This interaction does not occur at therapeutic concentrations within the patient because the drugs are diluted in plasma and body fluids.

Drugs formulated as acids – such as the hydrochloride form of basic drugs – are designed to maintain their solubility in aqueous solutions. However, when these formulations are mixed with drugs that are basic, or are added to basic vehicles, drug precipitation may occur.

Several drugs are not soluble in aqueous vehicles. Therefore they are dissolved in organic solvents (propylene glycol, polyethylene glycol for example), or alcohols. These are notoriously unpalatable to some animals, particularly cats. However, if these formulations are diluted in aqueous fluids, precipitation may occur. When these are stored at home by the pet owner, precipitation of the drug to the bottom of the container results in the dosing of a dilute mixture when the container is sampled from the top and a highly concentrated mixture when the container is sampled from the bottom (assuming that the precipitate at the bottom can be resuspended). This also may be observed when mixing some drugs in aqueous fluids. For example if diazepam solution (which contains propylene glycol and alcohols) is diluted in saline solution or Lactated Ringer's solution, precipitation occurs.

REFERENCES CITED AND ADDITIONAL READING