

THE REVOLVING CONCERNS OF DISPENSING AND COMPOUNDING

Dawn Merton Boothe, DVM, PhD, DACVIM, DACVCP

DISPENSING: Three issues should be of continuing concern. 1. Adulteration. Although the veterinarian community has not yet been impacted noticeably, adulteration of medications has made the headlines in the last year as a result of the addition of oversulfated glycosaminoglycans to heparin. 2. Counterfeiting: counterfeiting of products has become a major source of income for some populations (even replacing cocaine production). To date, the impact on veterinary medicine has not been addressed and is not known, but should be suspected simply because of its magnitude in human medication. Popular drugs are most commonly targeted. Counterfeiting is difficult to detect but might be minimized by using products for which the distribution trail can be documented, a process often impossible for internet based prescription filling. 3. A related internet dispensing issue is country of origin. Ethical products offer an example: the product may actually be approved in another country but appear very similar to the one approved in the USA. The former is illegal in the USA. Likewise, the filling of prescriptions through pharmacies in Canada does not assure that the product is Canadian. Products may actually be approved in a different foreign country for which the approval process is not as strict. 4. Human generic products. The use of an animal approved generic product should be undertaken with no concern if the approval of the original and generic drug is in the target species. FDA approval requires evidence of therapeutic and bioequivalence between the pioneer and generic products in the target species. However, a human generic product may not behave the same as the pioneer product behaves in a non-target species. Pharmacists are often legally empowered to switch generic products for their human patients and may do so with veterinary patients not realizing the implication regarding efficacy. Pharmacies are likely to use the least expensive of the generics and thus may intermittently switch. If the new product is more or less bioavailable than the former generic product, toxicity therapeutic failure, respectively, may occur. We are convinced this is a problem with cyclosporine and may be a problem with zonisamide (as well as any other human generic used in animals).

COMPOUNDING: Compounding has been defined by the National Association of Boards of Pharmacy (Model State Pharmacy Act) as the preparation, mixing, assembling, packaging, or labeling of a drug or device, as the result of a practitioner's prescription drug order (or initiative) and based on the practitioner /patient/pharmacist relationship (<http://www.iacprx.org/index.html>, accessed July 2004). The last two descriptors – prescription driven and in the context of a veterinary (client) patient relationship- are vitally important but often unrecognized or ignored descriptors of the definition. Compounding is and always has been a critical component to the provision of individualized drug care to the small animal patient. The Animal Medicinal Drug Use Clarification Act guarantees the right of veterinarians to compound. However, the science and art of compounding are also guaranteed to pharmacists, a profession more properly trained in pharmaceuticals (although not necessarily compounding). The sole justification for prescribing or dispensing a compounded preparation relates to the patient: no commercially available preparation is available which will meet the needs of the patient. Cost is NOT a justifiable reason for pursuing a compounded product. Many reasons exist for the veterinarian to use compounded products judiciously. These include legal and ethical reasons, all of which have been addressed in a comprehensive review of compounding for small animals (Vet Clin North Amer, September 2006; September 2006). Among the reasons are the lack of oversight by any state or (with the most recent federal court rulings) federal government oversight of the compounded product. Accordingly, no assurance can be provided regarding the quality, safety or efficacy of compounded product. Transdermal gels offer an example of both the best and worst considerations regarding the availability of novel drug delivery systems that are compounded.

Historically, drug use began with compounded medicinal agents, leading to the practice of pharmacy. Human compounding has undergone a dramatic swing for a variety of reasons, many economic, but others the need to individual drug therapy for special patient populations, such as geriatric and pediatric patients. Compounding has always been an important source of veterinary drugs. The lack of animal approved drugs, and the need for formulations for exotic or small animals mandated the need for compounding of veterinary drugs. However, compounding by pharmacists has taken a recent and dramatic upward turn. The growth of veterinary compounding has been a healthy adjuvant to the profession. The availability of compounding services enhances the veterinarian's ability to safely and effectively treat patients. Compounding may prove critical for certain species such as cats and exotics. Compounding can fill the need for previously prepared

antidotes for use in cases of animal poisonings. Compounding offers convenience. Under appropriate conditions, several drugs might be combined in a single dosage form for administration to a noncompliant patient. Novel drug delivery methods may allow more effective treatment – and safer administration – to fractious animals. However, the attributes of compounding also are balanced by detractors. Reformulation of any drug product into any compounded form, or the formation of a compounded product from pure drug should cause veterinarians to question the safety and efficacy of the product being dispensed or prescribed.

In the early 1920's, an unpatented sulfonamide antimicrobial was discovered. Within a short period of time, many manufacturers were making hundreds of sulfonamide antimicrobials. One of the products was prepared in ethylene glycol (antifreeze). Over 100 people – including children – died. At the time, no regulatory agency evaluated drug products prior to their market. However, this incident led to the Food and Drug Administration's role in the premarket assessment of drug safety. In 1968, the FDA assumed the role of assessing efficacy as well. Whereas approved animal or human drugs have undergone rigorous, scientific testing to ensure drug safety and efficacy for the patient, compounded products have not. Although pharmacists are directed to compound from written protocols and to maintain written records of compounding activities, currently pharmacists are not required to assure accuracy in product preparation, including product stability. Although a reputable pharmacy may randomly check accuracy of selected drugs, this act currently is voluntary and will be limited to selected drugs and aliquots. Although guidelines exist for establishing expiration dates of compounded products, dates are not necessarily based on scientific data and may not be followed. The risks associated with failed delivery (too much or too little) of a compounded product are added to risks associated with the approved finished dosing form of a drug. The more sophisticated the preparation, the more likely adverse events will occur because of diminished or excessive drug delivery. Few published reports exist that delineate adverse events resulting from inappropriate compounding. Despite indications of frequent problems with compounded products, the FDA receives few reports regarding adverse events related to compounded products. This reflects, in part, the lack of mandated adverse event reporting. However, it also reflects the difficulty in recognizing therapeutic failure due to failed delivery. The latter is likely to be detected only if it is sought and if the drug or response to the drug can be easily monitored. A variety of studies have focused on accuracy in labeling of compounded products, particularly in equine medicine. Products found to be mislabeled include omeprazole, ivermectin (both pirated drugs), ketoprofen (one product contained only 50% of the labeled content, whereas 12 of 13 contained close to 100%), amikacin (percent of labeled content ranged from 59 to 140%; none were within 10%), and boldenone (all within 15% of labeled content, but 2 of 5 contained up to 5% of impurities).

Potential Errors: Ingredient Errors: . Compounding from bulk substances is easier than from approved finished dosing forms because excipients or other materials do not interfere with product preparations. Further, excipients in the finished dosing form will not interfere with dissolution of the drug in the vehicle. However, the use of an approved finished dosing form of a drug for compounding offers a major advantage to use of a bulk substance in that the approved drug has passed stringent tests of analysis regarding drug purity and potency, and the absence of contaminants. As such, products formed from bulk substances are associated with greater risks compared to products compounded from approved drugs because the approved version has passed stringent tests of analysis regarding drug ingredients and presence of contaminants. In contrast, for bulk substances, the burden of purity and accuracy lies with the pharmacist and there is no mechanism to assure that the burden has been met. All products, active ingredient or excipients (fillers, preservatives, etc), domestic or foreign, should either meet United States Pharmacopeia (USP) or equivalent standards; or should be purchased after FDA inspection. However, bulk substances increasingly are being acquired by compounding pharmacies from non-inspected foreign (particularly Asian) sources at a price much lower than their domestic counterparts. Drugs which are still under US patents are often obtained in this manner. Bulk substances will be accompanied by a credible certificate of analysis. The need for validation of ingredient source (including all active and inactive substances) is paramount as inexpensive bulk substances increasingly are being acquired from non-inspected foreign (particularly Asian) sources. The active drug in a compounded product might also be substituted for an alternative drug; the substituted drug may not be characterized by the same pharmacokinetic or pharmacodynamic characteristics (also, see mathematical errors) and veterinarians should indicate on prescriptions that unapproved substitutions are not allowed for compounded products.

Mathematical errors. Mathematical errors are probably the most common reason for pharmaceutical compounding errors, and potentially the most lethal. Compounding is predisposed to mathematical mistakes because, by its nature (prescription driven, small volumes), much of the equipment and technology that facilitates accuracy and precision of finished dosing forms is not (should not be) used. In addition to the source of the ingredient, pharmacists may substitute drugs without acquiring clinician

permission. Mathematical errors may also reflect substitution of the active ingredient. For example, the content of active drug content may differ as is demonstrated by metronidazole. The recipe for metronidazole benzoate should contain 1.6 mg for each 1 mg metronidazole hydrochloride (or the dose must be similarly increased). Bromide offers another example: 1 gm of the sodium bromide contains more bromide (774 mg) than the potassium salt (692 mg). **Preparation and Storage Errors.** *Chemical reactions* (oxidation, reduction, hydrolysis) are facilitated by changes in humidity, light, pH, presence of oxidizing trace metals, and increasing environmental temperature.^{12,13} Excipients may enhance instability due to changes in pH or the presence of disintegrating agents. Degradation products (drugs or excipients) can cause adverse events. Excipients which are critical to the finished dosing form increase the risk of instability in product compounded from an approved source. Whereas approved products undergo intensive scrutiny in regards to stability and potency, compounded products do not; recipes for compounded preparations rarely are associated with studies that assure stability or delineate conditions for storage. Simple syrups (which tend to be acidic), preservatives, combination drugs, or other ingredients can alter drug pH, and thus, ionization (diffusibility) or stability. The more drugs mixed together in a single preparation, the greater the risk of chemical drug interactions. For example, weak acids and weak bases are likely to chemically inactivate one another. Interactions may occur between the drugs or excipients. For example, only 54% of a fluorinated quinolone (orbifloxacin) was found to be present when prepared in Lixotinic® as a vehicle compared to simpler syrups. **Particle size.** Compounding from approved drugs (legal) is more difficult than from bulk drugs (illegal) because excipients are more likely to result in undissolved macroscopic or microscopic precipitates which indicate undissolved and thus nondiffusible, ineffective drug. Sedimentation of undissolved particles may result in caking at the bottom of the drug receptacle; difficulty in shaking or rapid sedimentation (common) after shaking can result in erratic and unpredictable doses. Crushing of any oral tablet may result in unequal particle sizes in the preparation, which in turn will yield different surface areas and different rates of absorption. Fine crushing of the product such that it is no longer a suspension increases the concentration of soluble excipient; chemicals, including those added to the finished dosing form to facilitate degradation, can cause drug instability. Crushing an oral tablet for preparation in a syrup may also lead to unequal distribution of dissolved drug in the finished preparation and mixing the drug such that it is equally distributed throughout the preparation may not be possible. Repackaging oral tablets or capsules into smaller dosing units may also impact drug efficacy. Diluents such as starch and dextrose might impede oral absorption. Preparation of an oral formulation from an injectable solution is more inappropriate if the drug salt is different between the preparations. If the injectable product is presented in powder form, the drug is likely to be unstable in liquids and may be destroyed when added to liquid (oral solutions). The addition of flavoring agents to oral products may increase drug instability due to changes in pH or the increased risk of microbial growth (ie, with syrups).

Different Products: Altered release. Selected commercial oral preparations have been formulated to alter (slow or facilitate) drug delivery and reformulation of such products should be avoided. Compounding altered release products from bulk substances requires sophisticated techniques not generally available through pharmacists. Enteric coated or spansule products should not be crushed. Although spansule products might be reformulated without crushing, the amount of drug in each spansule is not necessarily predictable and random distribution of drug content is likely to yield erratic dosing. Cyclosporine is a complex molecule characterized by poor oral bioavailability; oral absorption requires bile acids or special formulation as a microemulsion product. As such, it is an example of a drug for which compounding should be approached cautiously, and be supported by therapeutic drug monitoring. In the author's drug monitoring laboratory, cyclosporine blood concentrations were not detectable (two different samples, two weeks apart) in one cat receiving a product compounded from an approved microemulsion human product. Following recommendations that the untampered animal approved version be used at the same dose, concentrations expected at the administered dose were detected within one week of the change in drug product.

Injectable products Administration of injectable products is inherently associated with a higher level of risk compared to administration of topical or oral products because of more rapid drug delivery, the risks associated with administration of suspensions rather than solutions, the potential impact of impurities (including endotoxin), and the need for sterility. Actions taken to assure sterility and removal of impurities may cause drug degradation. Endotoxin (which is essentially ubiquitous in the environment) is difficult to remove. Without testing, its absence is impossible to document, yet, its presence can be lethal. The USP has generated guidelines and state laws generally delineate regulations specifically for the compounding of injectable products. Veterinarians should be reluctant to prescribe compounded injections and when doing so, must be confident that the compounding pharmacist follows these criteria. **Topical products.** Although administration of topical products generally is associated with fewer risks compared to systemic

products (the exception would be ophthalmic products, which also should be sterile), compounding the proper product can be challenging. The USP has promulgated guidelines for the compounding of topical ingredients, including guidelines are designed to assure drug dissolution and drug movement from the vehicle into the skin. For example, solid ingredients should be reduced to the smallest reasonable particles size and the active ingredient should then be added to other substances necessary to dissolve the drug in order to achieve a uniform liquid or solid dispersion. Uniformity of dispersion should be demonstrated by spreading a thin film of the finished formulation on a flat transparent surface. Visual examination of a compounded product should be implemented to identify obvious problems with dissolution, etc. Care must be taken to assure ingredients are not caustic, irritating, or allergenic. Vehicle selection can be impressively difficult: undissolved drug can not pass into the skin; drug that has too great an affinity for the vehicle will remain in the vehicle. Transdermal gels offer an example where care must be taken with treatment of compounded preparations.

Ethical and legal issues surrounding compounding of veterinary drugs often differs from human products.

Compounding versus Manufacturing Unfortunately, often neither animal care givers, veterinarians or pharmacists may be aware of the differences between human and veterinary compounding. Compounding should be patient driven; drugs should not be compounded in large amounts in anticipation of compounding. Pharmacists may not be aware of the guidelines relevant to compounding, including the inappropriateness of manufacturing in anticipation. A number of pharmacies offer products that mimic commercially available products; indeed, the FDA has recently notified a number of pharmacists regarding the inappropriateness of compounding trilostane. Note that many pharmacies manufacture drugs, selling them in bottles that look like approved products, and distribute them through distributors. Potassium bromide (KBroVet) is an example of a compounded product that looks like an FDA approved product; indeed, the manufacturer reports that the product is made in an "FDA approved" facility (personal communication, author, August 2009). Ultimately, it is the veterinarian's responsibility - not the pharmacist's - to assure that compounded medications intended for the treatment or prevention of diseases in animals is both safe and effective. Accordingly, veterinarians must carefully consider the ethical, legal, and safety issues associated with use of compounded veterinary drugs. However, the pharmacist plays a major role in the assurance. The AAHA has recently endorsed a program intended to assure the quality of compounded products for both human and animals. The Professional Compounding Accreditation Board offers a program which, upon successful completion, allows a pharmacist to indicate their success (www.pcab.org).

Evidence of Efficacy: Transdermal Gels: Compounded transdermal pluronic-lecithin organo (PLO) gels have become a popular method of drug delivery widely embraced by the veterinary profession, despite the lack of scientific evidence in support of this system. The PLO gels were developed as a practical alternative to traditional drug delivery systems. Descriptions of the gels can not be found in the scientific literature but are limited to class materials and other non-referenced literature distributed to educators such as Professional Compounding Companies of America. The gels are comprised of water-based compounds prepared in various organic solvents. The oil phase is composed of lecithin (generally of soy bean origin) which theoretically re-arranges the stratum corneum, the major barrier to drug movement across the skin. Isopropyl palmitate acts as a solvent and penetration enhancer. The water phase is comprised of purified water and a pluronic (poloxamer) gel comprised of a surfactant (pluronic F127), which also contributes to disruption of the stratum corneum. The active drug ingredient is dissolved in either the oil (lipid) or water phase, depending on its lipid solubility. The amount of active drug added is based on the recommended dose; generally, the gel is designed such that the dose is delivered in 0.1 ml (cats and small dogs) to 0.5 to 1 ml (larger dogs). Lecithin and isopropyl palmitate (a ratio of 1:1) must comprise at least 24% of the system in order for micelles containing the drug to form properly. The remaining volume of a PLO gel is comprised of the drug and the pluronic gel. Because manufactured drug preparations often are not available in concentrations sufficient to allow delivery of the calculated dose in the small volume of PLO, purified bulk powder (which is not legal) is preferred by compounding pharmacies formulating the gels. When subjected to proper shearing forces (generally accomplished by rapidly passing the mixture between a small caliber catheter or two syringes). Micelles containing the drug theoretically are formed. The micelles are believed to slightly disorganize the stratum corneum with minimal direct detrimental effects on the skin (based on light microscopy), although contact hypersensitivity or allergy to the lecithin component may occur (see below).

The PLO gel appears to dissolve a variety of different chemicals, including lipophilic, hydrophilic and amphoteric compounds. The gels can be easily and rapidly prepared and theoretically are stable in most clinic environments. However, the gels are thermoreversible: at temperatures above 40°C, they are liquid, but they become high-viscosity gels following cooling to room temperature and remixing. At refrigerated temperatures, the gels again become liquid. Thus, the PLO gel becomes more viscous at

higher temperatures, rendering it more amenable to topical drug delivery. At least two PLO gels (ie, with the pluronic and oil phases already mixed) are commercially available: Lipoderm® is sold by Professional Compounding Pharmacies of America (PCCA). This organization offers compounding training classes for pharmacists, including formulation of PLO gels and recipes for the preparation of many different drug products as gels. The advent of PLO gels as a method of systemic drug delivery and the formulation of the original PLO gel was generated through the PCCA division of research. In addition to training, PCCA sells validated ingredients to be used in compounding. However, sale and compounding guidance is limited to PCCA members; membership at the time of publication of this article costs \$20,000. The financial incentive for PCCA to train pharmacists in the compounding of PLO gels intended for veterinary use is obvious. Products for formulation of PLO gels are also available through other companies (eg, Gallipot which sells a commercial PLO base as well as drugs, and chemical companies which sell pure drugs). The products that PCCA offers for sale has drawn the attention of the Food and Drug Administration: a warning letter was sent in 2001 regarding their sale of bulk substances, including dipyron and antibiotics. The availability of training in the preparation of PLO gels, and the level of promotion of gels by pharmacists suggests that this method of drug delivery has been validated scientifically. Yet, a review of the literature reveals little scientific support for the use of the PLO gel system and its ability to deliver drug.

Despite the lack of scientific validity, the number of compounding pharmacies that are offering compounding services, including formulation of PLO gels, is increasing as training in their preparation continues (eg, at PCCA). Recipes for veterinary PLO gels have been published in the International Journal of Pharmaceutical Compounding, a journal whose articles tend to focus on the sharing of compounding information rather than the reporting of scientific studies. The list of PLO drug recipes for veterinary use is extensive and includes but is not limited to nonsteroidal antiinflammatories, antimicrobials, anticonvulsants, prokinetic agents, anticancer drugs, behavior modifying drugs, and hormones. Scientific data regarding the use of PLO gels for systemic drug delivery is slowly becoming available. Methimazole is among the most common drugs formulated in a PLO gel for administration in cats and may be the most likely drug to be successfully delivered as a PLO gel because of its small molecular weight of 115 (compared to >250 for most other drugs). Additionally, response to therapy can be monitored. Other studies have confirmed the failure of the PLO drug delivery system to achieve therapeutic concentrations (and often detectable) in cats following single dose administration. These include amikacin, Enrofloxacin, morphine, fentanyl, diltiazem, fluoxetine, buspirone and amitriptyline. Follow-up studies following multiple dosing have revealed variable absorption among cats for amlodipine, atenolol, amitriptyline, prednisolone (no absorption with prednisone, metronidazole or enrofloxacin). Marked variability was found in the gels themselves, particularly for metronidazole and prednisolone.

The PLO gels offer other reasons that its use (as with other novel delivery systems) should be based on demonstrated efficacy using properly controlled studies. Topical reaction to the lecithin component have been reported with multiple dosing following experimental use of the gel in cats¹⁹. The compounded PLO product also offers an example of increased risk of drug exposure to the veterinary client. Clients should wear non-permeable gloves when administering the drug and counseled regarding inappropriate exposure of the drug to children or other pets.

This manuscript represents a portion of the paper Boothe DM: Veterinary Compounding in Small Animals: A Clinical Pharmacologist's Perspective published in Veterinary Clinics of North America, September 2006; and Drug-Induced Disease, Small Animal Clinical Pharmacology and Therapeutics, Boothe DM.

No portion of this manuscript can be reproduced without the author;s consent.