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Dr. Papich is a Past-President and Chairman of the Board of the American College of Veterinary Clinical Pharmacology. He also is a Fellow in the American Academy of Veterinary Pharmacology and Therapeutics and a member of the American Society of Clinical Pharmacology and Therapeutics (ASCPT). He was elected to the Council of Experts for the USP and is Chairman of the Veterinary Drug USP Expert Committee. He is the chairman and member of the Veterinary Antimicrobial Susceptibility Testing (VAST) subcommittee for the NCCLS and on the editorial board of three journals. He has given hundreds of invited lectures and is author or co-author of over 200 publications. His interests and expertise: pharmacokinetics, antimicrobial therapy, analgesic drugs, and analytical methodology.

- **Why are you interested in animal drug compounding and what harm have you seen from compounded medications?**

I have been a veterinary clinical pharmacologist for many years and have studied and written books on how drugs work in the treatment of diseases. As a consulting veterinarian in the specialty of clinical pharmacology and therapeutics in a teaching hospital I am frequently presented with cases referred to from other veterinarians where owners have been using compounded medications. They referred these cases to our clinic because the animals are not getting better and in many cases are in very poor condition when presented. I have tested many of these compounded products for potency in my laboratory and find that in many cases the drugs are well below the labeled concentration. I have also conducted my own research and presented findings in refereed scientific journals on the performance of compounded medications in animals. In practically all cases, these products are either not absorbed at all, or absorbed so poorly and inconsistently to be inadequate for treatment. We now have evidence that administration of antibiotics from these formulations that are sub-therapeutic can increase the risk of bacterial drug resistance, which is a risk both to the pet and animal owner.

In some cases the compounded products may actually contain levels well above the labeled amount which presents a risk of toxicity for the pet, as well as the animal owner handling the medication.

This unfortunate situation is occurring with increased frequency and we are also seeing an increase in antibiotic resistance in companion animals and horses which could be partially due to the use of sub- potent compounded antibiotics. Because compounded formulations are prepared in a manner that is inconsistent with the quality of FDA-

approved products, these formulations can degrade and disintegrate easily. Poor quality products risk exposure to humans handling the medication (insufficient coatings on tablets, or poorly packaged products, for example). Some products are designed to be applied to the ears of cats. Considering that it is a habit of cats to rub their ears on their human companions (especially children) the risk of human exposure is great.

I am very concerned that pet owners think they are doing the right thing and are distraught when they find out that they have actually prolonged their pet's illness by going to a compounder in order to save money.

- **Compounding pharmacies claim that there is no other way to deliver many medicines to animals without bulk compounding? Do you agree with that argument?**

  There are always alternatives in treating any disease. There are very few examples where only a single medication has been identified to treat a particular disease in animals. If a particular drug is not available other drugs in the same class may be approved as veterinary or human drugs. Human drugs can be prescribed by veterinarians and either used in the same dosage form for humans or could be altered by a compounding pharmacist in a formulation that would be easier to administer to an animal. In my opinion there are very few drugs that would be needed to be compounded from bulk active ingredients.

- **What research have you done on compounded medications and what have you observed?**

  I have been conducting research on medications for animals for 25 years. Many of these research projects have focused on appropriate delivery of medications to pets and exotic animals. I have presented this work at many scientific conferences.

  We have shown in independent studies that medications such as compounded antifungal drugs, antibiotics, and transdermal gels (gels to be applied to the ears of cats) are either unstable or inadequately absorbed in animals. An appendix to this document illustrates some of this research. In addition, other veterinary pharmacologists, like myself, have conducted similar studies and have reached similar conclusions. On the other hand, we have also shown that in some instances some compounding can be performed *appropriately* <u>if</u> *the compounding is performed by starting with an approved FDA product.* An example of this is from a study published by my laboratory in the Journal of the AVMA, July 1, 2013 (see Petriz et al) which showed that enrofloxacin can be effectively compounded if prepared from an FDA-approved product. Therefore, there is little need for the large number of products containing enrofloxacin compounded from a bulk source that appears in the catalogs of compounding pharmacies.

- **Where do you see a legitimate need for bulk compounding?**

  In almost all instances an effective compounded formulation can be prepared from an FDA-approved product. However, there are a few cases where there might be a need for bulk compounding for animals. These might be for exotic species, certain poison antidotes, and a few drugs which are simply not available for either veterinary or human use and no alternative exists. Such a list can be compiled easily using expertise that already exists in the veterinary colleges of the country and from reputable veterinary pharmacists.

- **What kind of controls should be considered?**

  Pharmacies should be prohibited from producing copies of approved products or complex dosage forms that often do not provide the correct amount of drug in the product, or they are formulated in such a manner that they do not deliver the targeted amount of drug to an animal patient. Compounding pharmacies make a claim that they can produce these medications with less expense than an approved pharmaceutical sponsor. They can make this claim because they use methods that do not meet compendial standards, inadequate controls, lack of standardization, and they do not include critical ingredients (excipients) or packaging that is important to drug stability, shelf-life, and absorption in animals. Preparing an effective medication is not as simple as combining a powdered bulk active ingredient with some other inactive ingredients and expecting the formulation to perform effectively. Pharmaceutical scientists spend a career learning these methods, and pharmaceutical companies spend millions of dollars and many years perfecting formulations that can stand up to the needs of veterinary patients. Federal regulations for approval of safe medications, and the creation of the agency (FDA), were established for a reason: to assure the public that pharmaceutical dosage forms can be relied upon to produce consistent results. FDA could establish a discrete list of compounds suitable for bulk compounding but controls should be in place such as following USP monographs if they exist.

- **Compounders claim that an FDA positive list would lead to rampant deaths of dogs and cats because veterinarians couldn't get needed drugs. What is your response?**

  As I noted before, there are far more animal health problems associated with the use of compounded products than not having a compounded product available. I have yet to hear of a legitimate example in which a dog or cat would suffer if a compounded drug from a bulk source was not available. There are very few drugs that could be identified as truly life-saving. Such a list can be prepared and would provide guidance to pharmacists that these medications could only be made available through bulk

compounding and would likely be on any positive list that was developed with stakeholder input. But the truth is that there are numerous pharmaceuticals available in human dosage forms that can fill most animal treatment needs even those of critical medical nature.

- **Compounders have argued that transdermal gels must be made from bulk API's and are essential for medicating cats. Do you agree?**

  As illustrated in some examples provided in the Appendix, transdermal gels made from bulk API are not absorbed in cats, but for one exception (methimazole). The skin is an efficient barrier and it is very difficult to facilitate the absorption of most drugs through the skin. Development of transdermal technology in animals is very difficult otherwise pharmaceutical companies would have developed many products in this form. I have researched these products and my conclusion is that they are erratic as far as drug absorption in to the body and therefore do not attain consistent therapeutic blood or tissue concentrations. Most compounded transdermals for animals are at best placebos. Because of the lack of effective absorption when these products are applied to the ears of cats, it presents a risk of exposure to the family of these pets, especially children. It is a common habit of cats to rub their ears against their owners and on furniture and bedding.

  It is true that cats can be difficult to medicate but there are ways to make up flavored oral suspensions of tablet forms of an approved drug which are easier for owners to administer.

- **Compounding pharmacies have claimed that they can't use approved products to compound a new formulation because of the narrow window of 90-110% active ingredient concentration that FDA requires on approved products. Is this true?**

  This is a false argument. The range of 90-110% applies to the nominal amount contained in a formulation. If a formulation is compounded from an approved formulation, the compounding pharmacy is only responsible for meeting a range of 20% (+/- 10%) of the theoretical amount in the formulation. If the compounding pharmacy is following proper procedures this range is attainable. There are no credible scientists that would accept a range of greater than 20% for assurance of a medication, and pet owners should not be expected to accept such a substandard product for their animals.

- **Pharmaceutical companies have been accused of obtaining approval of a commonly available compounded drug and then raising the price on the approved product to many times higher than the compounded version. What is your view of this?**

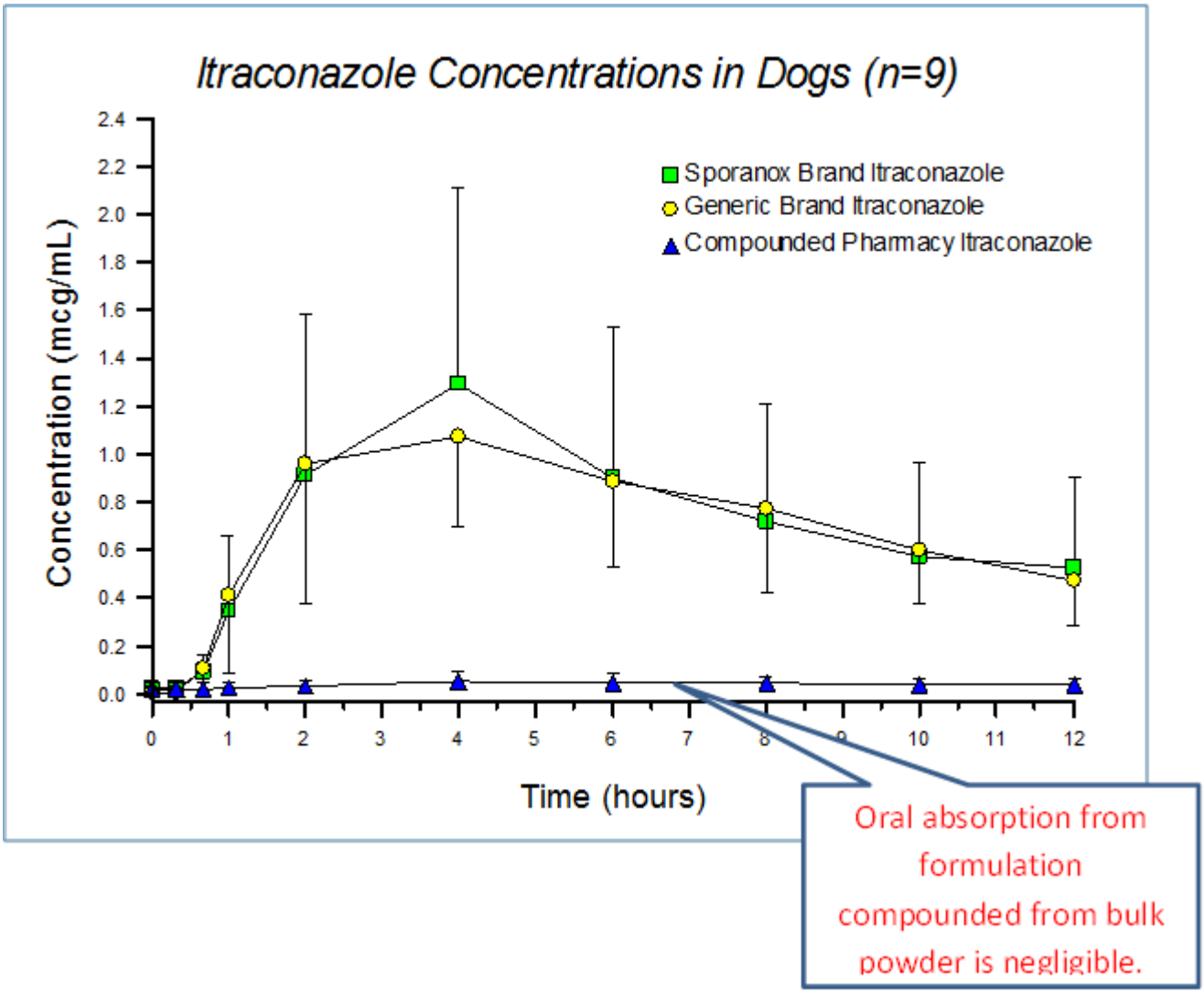
There are no examples in which this has occurred. Compounding pharmacies prepare medications based on the success of an approved product that has already been approved and marketed. In some instances compounding pharmacies copy a formulation that is approved in Europe prior to its approval in the U.S. (example: pimobendan and trilostane). This practice creates a disincentive for pharmaceutical sponsors to invest in research and development to bring a successful drug to market.

This argument also assumes that the public will accept a reduced price product as a trade-off for an assurance of safety and efficacy. I have encountered many examples in which a pet owner eventually paid a lot more for extended care and treatment of a pet because an ineffective or unsafe compounded medication was initially prescribed.

A compounded medication can of course be produced at pennies on the dollar compared to what a drug company must charge to recoup the enormous investment in taking the product through the FDA approval process. However, there is no assurance that the compounded product is safe or effective so any cost savings comes at a great risk to the health of the patient and in my opinion is not worth the risk.

**Addendum:**

SUMMARY OF RESEARCH




Itraconazole, an important antifungal agent, is frequently compounded from bulk powder by compounding pharmacies in order to sell at a reduced cost. However, in this study presented at the 2013 ACVIM scientific forum by D. Mawby & M.G. Papich showed that the compounded version had negligible oral absorption (publication is pending).

## EXAMPLES OF POTENTIAL PROBLEMS

There are several relevant 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) (Nieto et al, 2002). Systemic concentrations of the compounded formulation were not as high as for the proprietary product. Omeprazole is known for its instability unless administered in the original formulation intended for horses or people. Other medications prepared for horses have shown poor quality and inferior potency when prepared by compounding pharmacies. These were summarized by Dr. Scott Stanley of the University of California (see attachment). The drugs in his study included anabolic steroids, antibiotics, and anti-inflammatory drugs.

## TRANSDERMAL DRUGS

**Studies in which poor absorption has been confirmed through study of compounded transdermal gels for cats**: (partial list)

Diltiazem (Nolan et al)
Buspirone (Mealey et al, 2003)
Amitriptyline (Mealey et al, 2003)
Fluoxetine (Ciribassi et al, 2003)
Dexamethasone (Willis-Goulet et al 2003)
Glipizide (Bennet et al, 2005)
Methimazole (Hoffman et al, 2002)
Morphine (Boothe et al. ACVIM 2005)
Fentanyl (Boothe et al. ACVIM 2005)
Enrofloxacin (Boothe et al. ACVIM 2005)
Atenolol (MacGregor, ACVM, 2006)

The administration of transdermal drugs to animals was reviewed by Riviere & Papich in 2001. Because of success with some transdermal drugs (antiparasitic agents and fentanyl) there is considerable interest in formulating a wide range of other drugs for this route. Compounding veterinary pharmacists advertise the ability to formulate transdermal medications from existing forms of antibiotics, cardiovascular drugs, antithyroid drugs, analgesics, corticosteroids, and antidepressants. Bulk drugs also have been used for transdermal compounding. Drugs have been combined with penetration enhancers to facilitate transdermal absorption. One popular example of a penetration enhancer, is pleuronic lecithin organogel (PLO), which is lecithin

(derived from eggs or soybeans) mixed with isopropyl palmitate and a poloxamer (Pluronic). The ingredients in PLO act as surfactants, emulsifiers, and solubilizing agents. Although the use of PLO is popular among the veterinary compounding pharmacies, there are no successful commercial formulations that have combined PLO with systemic drugs. Usually, animal owners are instructed to apply the drug to the inside of the animal's ear because this location cannot be licked with the tongue, and it is usually not covered with hair.

Published reports (some co-authored by Dr. Papich) of transdermal application of drugs to cats showed that absorption was incomplete, nonexistent, or highly inconsistent among cats. Yet, some pharmacies widely advertise their willingness to provide these formulations to veterinarians via the internet and promotion at national trade shows. Drugs examined so far have included glipizide, dexamethasone, buspirone, amitriptyline, fentanyl, morphine, fluoxetine, and diltiazem. (Nolan et al, 2002; Hoffman et al, 2002) Glipizide was absorbed poorly in some cats and only 4-30% compared to oral in others. Fluoxetine was absorbed only 10% but if a large dose was administered (10 x oral dose), plasma concentrations equal to oral dosing was achieved (Ciribassi, et al, 2003). Repeated application of fluoxetine caused dermatitis. Methimazole was not absorbed well according to a pharmacokinetic study (Hoffman et al, 2002; Trepanier 2002), but produced clinical efficacy in some animals with repeated transdermal application in other studies (Hoffman et al, 2001). When dexamethasone was administered topically in PLO, there was negligible absorption in cats (Willis-Goulet, et al 2003). Results of other studies have been presented at scientific conferences. It is important to understand that these medications represent a vast variety of drugs with different chemical properties (solubility, potency, and drug class), yet they all demonstrated the same inferior performance.

The most common concern is lack of efficacy of these formulations because of poor absorption or decreased stability of the formulated drug. However, increased risk of toxicity also is a potential problem. If the drug is ordinarily poorly bioavailable after oral administration because of a large first-pass effect, higher systemic levels after transdermal application may result. Obviously, there also is a risk to the animal owner applying the medication if the drug is toxic to humans.

## ADDITIONAL READING


Ciribassi J, Luescher A, Pasloske KS, Robertson-Plouch C, Zimmerman A, Kaloostian-Whittymore L. Comparative bioavailability of fluoxetine after transdermal and oral administration to healthy cats. Am J Vet Res. 2003; 64(8): 994-998.

FDA-CVM. Compliance Policy Guide: Compliance Policy Guidance for FDA Staff and Industry. Chapter 6, Subchapter 600, Sec. 608.400 – Compounding of Drugs for Use in Animals, July 2003. Food and Drug Administration, 5600 Fishers Lane, Rockville MD. http://www.fda.gov/ora/compliance_ref/cpg/default.htm or http://www.fda.gov/OHRMS/DOCKETS/98fr/03d-0290-gd10001.pdf.

Hoffman SB, Yoder AR, Trepanier LA. Bioavailability of transdermal methimazole in a pluronic lecithin organogel (PLO) in healthy cats. J Vet Pharmacol Therap 25: 189-193, 2002.

Hoffman G, Marks SL, Taboada J, et al. Topical methimazole treatment of cats with hyperthyroidism. J Vet Intern Med 15: 299, 2001.

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Nieto JE, Spier S, Pipers FS, Stanley S, Aleman MR, Smith DC, and Snyder JR. Comparison of paste and suspension formulations of omeprazole in the healing of gastric ulcers in racehorses in active training. J Am Vet Med Assoc. 2002; 221(8): 1139-1143.

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Willis-Goulet HS, Schmidt BA, Nicklin CF, et al. Comparison of serum dexamethasone concentrations in cats after oral or transdermal administration using Pluronic Lecithin Organogel (PLO): a pilot study. Veterinary Dermatology 14: 83-89, 2003.