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FOCUS ON

What You Should Know About Compounding

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Compounding is an established healthcare practice that enables clinicians to prescribe medications that are patient specific, both human and veterinary. Compounding denotes any manipulation of a drug beyond what is specified on the drug label and can include mixing, diluting, concentrating, flavoring, or changing the dosage form.¹ This practice is followed when an equivalent commercially manufactured product is not available due to strength, formulation, or inclusion of inactive ingredients.

For small animals, medications are often not available in an appropriate formulation, rendering compounding necessary to achieve an appropriate dosage strength for treatment. However, the safety of compounded formulations is not evaluated by the pharmacy preparing the compound or by the U.S. Food and Drug Administration (FDA). Compounded medications either use an FDA-approved medication that is commercially available and alter it to meet the patient's needs or use the FDA-approved medication's active ingredient as a bulk chemical. Other medications that are frequently compounded and used (e.g., cisapride) are not considered legal compounds as denoted by the FDA because they use active pharmaceutical ingredients or bulk chemicals for which there is no FDA-approved product commercially available. Although federal regulations provide guidelines for the preparation of

compounded medications, there is not sufficient oversight and compounders may use bulk powder even when tablets or capsules are commercially available.

Because there are not enough drugs approved for veterinary use to meet the needs of every patient, use of compounded medications is an essential tool in veterinary medicine; as a result, human-approved medications are often used. According to a 2020 study, the median cost to bring a drug to market is \$985 million.² Although it costs significantly less to bring an animal drug to market, these costs can still be insurmountable, which limits the development of new animal drugs. According to the American Veterinary Medical Association, central reasons why there are fewer approved veterinary medications include the cost and the time it takes for FDA drug approval; the return on investment for animal drug products is small compared with that for human drug products.³

REGULATION OF COMPOUNDED MEDICATIONS

The FDA and state governments have been tasked with working together to regulate the practice of compounding, but the reality of whether this occurs is up for debate. Regulation of compounding for veterinary patients stems from the Animal Medicinal

Be aware of your state's specific restrictions and requirements relating to compounding for in-office use for veterinary patients and of any special provisions relating to compounding.

Drug Use Clarification Act of 1994,⁴ which describes the regulations for compounding medications for companion and food animals. Compounding for food animals, however, is far more stringent than compounding for companion animals and should be reserved as a last resort. With regard to the regulation of practice, each state board of pharmacy has been delegated with the primary responsibility of supervising day-to-day pharmacy practices, including compounding, and the state veterinary medical boards oversee veterinary medicine. In practice, it may not be possible for state boards to oversee the ever-growing compounding pharmacies under their jurisdiction. Compounding laws and regulations, as well as which agency oversees veterinary compounding, differ between each state. Be aware of your state's specific restrictions and requirements relating to compounding for in-office use for veterinary patients and of any special provisions relating to compounding.

Compounding pharmacies are required to register as either 503a or 503b. A compounding pharmacy's website should clearly indicate if the pharmacy is designated as a 503b; otherwise, one can assume that it is a 503a pharmacy.⁵

503a pharmacies compound according to prescriptions specific to particular patients and are required by state boards of pharmacy to comply with United States Pharmacopeia (USP) and other guidelines. These facilities are limited to dispensing for individual patient use only and are not allowed to compound large batches. Most small, independent pharmacies register as 503a because their focus is patient-specific compounds. This registration prohibits them from compounding and distributing compounded medications in bulk for in-office use. Because the Drug Quality and Security Act exempts veterinary patients, the applicability of this registration to veterinary medicine is questionable; therefore, in-office use is still regulated by states and is highly variable.

503b pharmacies are termed "outsourcing facilities" and have the ability to manufacture large batches with or without prescriptions that can be sold to healthcare facilities for in-office use. Larger compounding pharmacies have the opportunity to voluntarily register as 503b. These regulations are much stricter because they are regulated by the FDA instead of the state and require facilities to follow current good manufacturing practices. These facilities manufacture compounds that are prepared in the same manner as commercial products but that have not been evaluated for safety and efficacy by the FDA. When a compounding pharmacy offers both 503a and 503b products, it is in the best interest of veterinarians and their patients to select 503b products. As well as being more strictly regulated, they often offer an extended beyond-use date, which makes them more appealing. 503b facilities are required to test products from every batch to ensure that they contain the drug and quantity listed on the label. If the product is designed to be sterile, sterility must also be tested. This testing increases the end-user's confidence in the quality of the final product.

TABLE 1 Compounded Medications for Which Studies Have Indicated Concerns

COMPOUNDED MEDICATION	CONCERN
Cyclosporine	Deviates >10% from approved product; bioavailability and clinical efficacy unknown. ⁶
Doxycycline	Drug content is extremely variable in products. ⁷
Fluconazole	Drug content is extremely variable in products. ⁸
Itraconazole	Is less orally bioavailable than the approved product. ^{9,10}
Lomustine	Drug content is extremely variable in products. ¹¹
Omeprazole (paste)	Preparations may not be equally effective as commercial product. ¹²
Trilostane	Bulk chemical has lower dissolution and may lead to variable bioavailability in products. ¹³

SAFETY AND EFFICACY OF COMPOUNDED MEDICATIONS

Compounded medications can be extremely beneficial to patients, but they are not without risk. Compared with commercially manufactured products that have been approved by the FDA, compounded products pose a greater risk to the patient's health. Some examples are provided in **TABLE 1**. Many products that are available from compounding pharmacies do not meet USP standards, have not been shown to be effective, or can be harmful for the patient. Although evidence indicates that these products do not meet the standards for bioequivalence to approved products, they are still promoted by compounding pharmacies.

Transdermal medications have become increasingly popular for feline patients, but no data support use of most of these products (**TABLE 2**). Medications that should never be compounded for transdermal delivery include antibiotics, those that have an effect within the gastrointestinal tract, and any that are cytotoxic.

WHEN TO USE A COMPOUNDED MEDICATION

The decision to use a compounded preparation should be veterinarian driven and should always be made according to evidence-based medicine.¹⁵ However, many compounding pharmacies use flyers and email to promote use of compounded medications over commercially available products, even if a compounded medication is not medically required. Compounded medications should not be used unless FDA-approved drugs are not sufficient, as that would be considered a type of extra-label use.

Reasons to Use Compounded Medications

There are a variety of reasons for prescribing a

compounded medication as opposed to a commercially available medication.

- The patient needs medication at a strength that is not commercially available.
- The patient needs medication in a dosage form that is not commercially available.
- The commercially available product contains a substance that is toxic to the patient or to which the patient is allergic.
- Compounded medication may be easier to administer.

Compounded sildenafil provides an example of ease of administration. The size and composition of the commercially available 20-mg tablet can cause the tablet to crumble when quartered, leading to loss of some of the medication. Instead, for treatment of pulmonary hypertension, feline patients can receive a maintenance dose of 0.25 to 1.6 mg/kg of compounded sildenafil suspension orally q24h (off-label).¹⁶ The appropriate dose of the compounded oral suspension can be drawn up into a syringe; thus, veterinarians can be far more confident that the cat will receive the appropriate dose. In addition to content uniformity of the compounded oral suspension, a flavored suspension may make medicating the patient easier for the client, thereby increasing compliance.

Reasons Not to Use Compounded Medications

Some reasons for prescribing compounded medications are inappropriate. One such reason is that compounded medication may cost less than the manufactured product. Some compounding pharmacies may be able to offer compounded medications at a lower cost than the commercial product because they use bulk chemical powder to create their formulation. However, cost should not drive your patient's treatment options.

TABLE 2 Potential Classwide Concerns About Transdermal Therapy¹⁴

DRUG CLASS	POTENTIAL CONCERN	RECOMMENDATION
Antibiotics	Low blood levels can lead to resistance	Avoid transdermal use
Corticosteroids	Can cause atrophy of the pinna	Discuss risk/benefit with caregiver
Gastrointestinal medications exerting only local effects	Will not reach site of action	Avoid transdermal use
Hazardous medications	Pose risk to caregivers	Discuss risk/benefit with caregiver
Medications with narrow therapeutic index	Increase risk for toxic levels and ineffective levels	Avoid transdermal use

When a compounding pharmacy offers both 503a and 503b products, the better choice is 503b because of more stringent regulation and testing.

Legal entities, such as the FDA, prefer that commercially available products be used because these entities oversee the verification of their safety, effectiveness, and quality before the products are marketed. As mentioned previously, the FDA, along with the state boards of pharmacy, is obligated to monitor compounding practice; however, whether this obligation is fulfilled is in doubt. In compounding pharmacies, on both the human and veterinary sides, compounded products are often formulated from bulk chemicals instead of commercially manufactured products. The concern with this practice is that compounded medications have not been proven to be safe or effective to the standards of a commercial product, and in the case of 503a pharmacies, proof of quality is not required.

FINDING A COMPOUNDING PHARMACY

Given the growing number of pharmacies that participate in compounding of both human and veterinary products, assessing the quality of compounded medications is imperative. First, ask your state board of pharmacy for a list of licensed compounding pharmacies. Also, the Pharmacy Compounding Accreditation Board assesses pharmacies for compliance with USP standards. By achieving this accreditation, a pharmacy shows commitment to compliance for preparing compounded medications and demonstrates interest in meeting standards for quality and safety. Achieving accreditation involves an inspection and a fee, and compounding pharmacies can choose whether or not to pursue this voluntary and expensive option. Other sources for finding a compounding pharmacy include compounding organization websites. The Alliance for Pharmacy Compounding has a pharmacy locator for compounding pharmacies (a4pc.org/apc/findacompiler.aspx). The American College of

Apothecaries also has a pharmacy locator for any pharmacies registered as members (acainfo.org/pharmacylocator). The pharmacies on these lists should still be assessed for quality standards, extent of staff training, how they compound their medications, and whether they are accredited.

Before calling in a compounded prescription to a 503a pharmacy or sending a client with a prescription for a compounded medication, do your due diligence and ask the pharmacy a few questions about their compounding practices. Determine if they are compliant with USP standards, which include chapters <795> for nonsterile compounding, <797> for sterile compounding, and <800> for hazardous compounding. If there are USP formulations available, they should be using USP monographs. If they are not, you can ask where they obtain their formulas. Compounding companies have specialists that can provide formulas, including the Professional Compounding Center of America and Medisca; in addition, multiple journals publish compounding formulas (e.g., *International Journal of Pharmaceutical Compounding*).

SPECIAL CONSIDERATIONS

Pharmacists are specifically trained in the pharmacodynamics and pharmacokinetics that affect humans but receive little to no training for veterinary patients. Recently, pharmacy schools have started recognizing the prominence of compounded medication use for veterinary patients and some have added training to their elective curricula. However, it is crucial to confirm with the pharmacy that they are familiar with veterinary-specific compounding and familiar with restrictions on ingredients for veterinary patients (e.g., toxicity of xylitol for dogs). When prescribing a medication, be sure to specify a flavor for the patient because the pharmacist may not be familiar with preferential flavors of veterinary patients beyond cats and dogs. If you are interested in getting a particular medication compounded into a certain strength or dosage form, reach out to a compounding pharmacy and ask about the availability of a formula. They should be able to discuss if it is feasible or should provide you with other potential options.

SUMMARY

- Compounded medications can be useful when FDA-approved medications are not available.
- Choose a compounded medication when a commercial

product is not available, is toxic or allergenic for a given patient, or is difficult to administer.

- Do not choose a compounded medication on the basis of cost only.
- When a compounding pharmacy offers both 503a and 503b products, the better choice is 503b because of more stringent regulation and testing.
- Consider the risks of compounded medications, especially those for transdermal delivery.
- Assess the quality of compounding pharmacies and their compounded medications. **TVP**

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