

Legal and ethical veterinary compounding

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Food and Drug Administration

The Food and Drug Administration (FDA) first made a distinction between human and veterinary-labeled drugs in 1968. As with most regulations since that time, the distinction reflected a concern for human food safety. At that point in time, an animal drug was adulterated if used in an extra-label manner. Consequently, veterinarians were not permitted to use any drug except according to the label claim, without being in violation of both criminal and civil law. In an ideal world, pharmaceutical dosage formulations would exist to treat all disease conditions in humans as well as all species of animals. The economic reality does not permit the establishment of numerous pharmaceutical solutions for most disease states and relatively few pharmaceuticals have been developed for animal species. The development of a new animal drug typically averages ten years and cost \$40 million. This combined with the narrow profit margins for most products makes for a challenging market place.

By definition, a New Animal Drug is “any drug intended for use in animals other than man...”.^{1,2} Veterinarians must by necessity on occasion utilize products that are compounded to meet a specific medical need. However, the AVMA guidelines for pharmaceutical compounding state that compounded products “may be used only when a need has been established and FDA-approved products are not available or clinically effective.”^{2,3} While FDA-approved products are extensively tested for efficacy, quality,

purity, strength, bioavailability, and stability, the testing that compounded formulations are subjected to is extremely variable.

The FDA's Center for Veterinary Medicine (CVM) allows for the compounding of animal drugs under the 1994 Animal Medicinal Drug Use Clarification Act (AMDUCA).² This Act became a law in 1996 and extended the veterinarian's authority to use human drugs in an off-label manner, including the right to compound with the use of FDA-approved dosage forms. AMDUCA does not allow for the compounding of drugs from bulk active substances, and any products resulting from such substances are considered new animal drugs and are subject to the FDA drug-approval process.

The FDA Modernization Act of 1997 allows for the compounding of human drugs from bulk chemicals as long as the bulk substance is an ingredient of a currently approved product that appears on an FDA list of drugs that can be compounded.³ It is important to note, however, that ingredients that are on the list of bulk substances withdrawn from the market for safety reasons may not be compounded. Human compounding regulations are sharp contrast to current animal compounding regulations. These regulations become an important consideration for veterinarians who out-source compounding to pharmacies that may compound exclusively from bulk active chemicals. Bulk chemicals are defined as active ingredients used in the manufacture of finished dosage forms of the drug. Bulk chemicals are also referred to as the active pharmaceutical ingredients (API). Compounding from bulk is allowed in instances where the health of the animal is at risk and there are no other remedies.

Drug: The FDA defines a drug as any substance, food or nonfood; intended for diagnosis, cure, mitigation, or prevention of disease in humans or other animals; intended

to affect body structure or function; or any substance administered by injection.³ This broad definition effectively means that any substance used to treat an animal can be considered a drug.

Veterinary Compounding

Drug compounding can be defined as the art and science of mixing ingredients, which may be active, inactive or both, to create a specific dosage form to meet a particular patient's needs. For example, mixing two injectable drugs is compounding.

Compounding can be performed by a veterinarian, or by a pharmacist upon receipt of a veterinarian's prescription for a particular patient. A veterinarian must have a valid veterinarian-client-patient relationship in order to legally prescribe or prepare a compounded product. Federal regulations require that legally compound drugs meet the following criteria:³

- A valid Veterinarian-Client-Patient relationship (VCPR) must exist.
- The health of an animal must be threatened or suffering or death may result from failure to treat.
- There must be no FDA-approved, commercially available animal or human drug that, when used as labeled or in an extra-label fashion in its available dosage form and concentration, will appropriately treat the patient.
- The product must be made from an FDA-approved commercially available animal or human drug.

- The product must be compounded by a licensed veterinarian or a licensed pharmacist on the order of a veterinarian within the practice of veterinary medicine.
- The compounded product must be safe and effective.
- The amount of product compounded must be commensurate with the need of the animal identified in the VCPR-based prescription.
- For animals produced for human consumption, the veterinarian must establish an extended withdrawal interval for the compounded product and ensure food safety. Compounding is not permitted if it results in violative food residue, or any residue that may present a risk to public health.
- No drug may be compounded for food animals from drugs listed on the prohibited list.
- Veterinarians must comply with all aspects of the federal extra-label drug use regulations including record-keeping and labeling requirements.

Pharmacies specializing in veterinary compounding have been growing exponentially aided by the ability to reach a larger number of consumers via the Internet. Many commercial websites market directly to the owner offering subjective treatments based on testimonials and compounded therapies that are not permitted by the criteria established for compounded drugs. Currently, the FDA does not have the resources to enforce these regulations; however, veterinarians should be aware that abuse of these regulations can result in legal action (e.g., FDA warning letters, confiscation of inventory and other enforcement action). The FDA has determined that it will seriously consider taking action

when the scope and nature of activities of veterinarians and pharmacists raise concerns normally associated with a drug manufacturer resulting in significant violations of the new animal drug, including adulteration, or misbranding.

Compounded drugs are not the same as generic drugs. Generic drugs are FDA-approved. To receive FDA approval, generic drugs must demonstrate bioequivalence to the "pioneer brand name" drug. Generic drugs can be identified by the ANADA number on their label and by cross-checking with a drug reference found in the FDA Green Book of Approved Animal Drug Products. In contrast, compounded drugs are extemporaneously prepared products that lack FDA approval.

The idea is that compounded drugs with their possible inadequacies are better than no drug at all and suitable for a small patient population. Equine practitioners using compounded products are put in a position of evaluating the integrity of the compounding pharmacy as well as the quality and consistency of the pharmaceuticals they produce. Lack of regulatory approval means that not all veterinary compounding pharmacies follow Good Manufacturing Practices (GMPs) Guidelines simply because they are not required to. In some instances, loose oversight has allowed negligent compounders to prepare products from unregulated raw materials with no quality standards. Other compounding pharmacies distribute medication without a valid prescription. Veterinarians are schooled on quality patient care but few pharmacists are. Veterinarians who frequently use compounded products would be well advised to learn more about pharmacy issues related to veterinary medical therapy.

For example:

- It is illegal to compound a specific product when there is an approved drug form of that specific product, except to make a different dosing form. However, the approved product must be used to make the compounded new dose form.
- It is illegal to mark up prices on compounded drugs
- As a veterinarian, if you use a compounded product, you assume liability for any adverse effects or efficacy failure.
- Drug manufacturers are required to carry product liability insurance, pharmacies are not
- It is illegal to place expiration dates on compounded products
- It is illegal to have a drug compounded in order to obtain the drug at a lower price

Problems and concerns regarding the use of compounded drugs

Omeprazole . This study was undertaken to determine the efficacy of commercially available omeprazole paste and a compounded omeprazole suspension to heal gastric ulcers.⁴ Results from this study suggested that while administration of the commercially available omeprazole formulation was effective in promoting healing of gastric ulcers in horses, administration of the compounded omeprazole suspension was ineffective. Differences in the source of omeprazole and partial inactivation of omeprazole by the vehicle or by gastric contents following administration of the suspension were cited as possible reasons for the poor results seen with the compounded product.

Pharmaceutical equivalence. The pharmaceutical potency of compounded preparations of ketoprofen, amikacin and boldenone were compared with commercially

available FDA approved products.⁵ The FDA requires any manufactured pharmaceutical to have a concentration (potency) of not less than $\pm 10\%$ of the expected concentration as stated on the product label. The results of this study found that 11 of the 22 compounded products failed to meet the FDA requirement for potency. Of the eleven products that failed to meet the FDA standard, the range in percentage potency was as low as 50% and as high as 150% of what was stated on the prescription label.

Compounded clenbuterol. In 2006, concentrated counterfeit clenbuterol was determined as the cause of death for several Thoroughbred horses in Louisiana. The compounded clenbuterol solution was analyzed and found to be extremely potent, ~70 times greater than the FDA approved commercial product Ventipulmin® (Boehringer Ingelheim Vetmedica, Inc, St. Joseph, MO USA). The source of the compounded clenbuterol solution was not determined but the trainer stated the product was "...just like Ventipulim® but cheaper...".

Compounded chloramphenicol palmitate. Six owners sued a New Jersey veterinary pharmacy alleging that a defective antibiotic led to the deaths of three horses, including Saratoga County and Egg Head, both stakes winners. They alleged negligence, breach of warranty, and strict products liability against the pharmacy involving the antibiotic product chloramphenicol palmitate, that they claimed necessitated the euthanasia of three horses. The case cites improper design, manufacture, compounding, formulation, mixing and/or labeling, (which) "led to the slow, painful demise of these horses." Following a two year legal battle the case was dismissed by the United States District Court in New York.

Conclusion

Products are required to treat hundreds of conditions and diseases in dozens of species. Compounding of drugs for use in animals is a necessary and beneficial component of veterinary practice. Licensed veterinarians may legally use or dispense prescription drug products ONLY within the course of their professional practice where a valid VCPR exists. FDA Compliance Policy Guides permit licensed practitioners to manufacture, prepare, propagate, compound or process drugs during the regular course of business, as long as the compounded product is NOT a new animal drug.

References:

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