

Introduction

Compounding animal preparations to address disease conditions in animals is an integral part of veterinary medicine. The animal health industry supports compounding permitted by federal law, which is the manipulation of an approved drug by a veterinarian or pharmacist upon the prescription of a veterinarian to the needs of a particular patient. In addition, we support FDA's use of enforcement discretion to allow compounding from bulk drug substances where an active pharmaceutical ingredient needed to treat a patient condition is not contained in an approved drug.

Necessary and appropriate limits on this enforcement discretion are described in Draft Guidance for Industry #256. Some compounders, who act like manufacturers by making large quantities of compounded preparations from bulk drug substances and marketing them as less expensive alternatives to approved drugs, have made several misleading and nonfactual claims about this guidance document. This document addresses those misleading claims.

Claim: FDA does not have statutory authority to set forth parameters around compounding animal drugs from bulk substances.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives authority to the FDA to oversee the safety of drugs. Compounding of animal drugs from bulk drug substances results in new animal drugs that must comply with the FD&C Act's approval/ indexing requirements. This fact has been upheld by every Federal Court of Appeals that has considered the issue. This authority is clearly explained by FDA in Guidance #256.

While the law clearly charges the FDA with protecting the public from illegal drugs, there are no statutory provisions in the FD&C Act that support compounding from bulk drug substances for veterinary use.

Claim: It is legal to produce compounded drugs from bulk substances.

FDA clarified that "No, [it is not lawful to compound animal drugs from bulk drug substances under federal law]. The Federal Food, Drug, and Cosmetic Act (FD&C Act) does not distinguish between compounding animal drugs from bulk drug substances and any other manufacturing or processing of animal drugs. Compounding an animal drug from bulk drug substances results in a new animal drug that must comply with, among other things, the FD&C Act's approval and indexing requirements." Decisions from three federal appeals courts support this conclusion.

Claim: GFI #256 contradicts existing state law which allows veterinarians to exercise their medical judgment to compound or order compounded medication for veterinary office use.

There is a big difference between compounding drug from FDA approved medicines and compounding a drug from bulk substances. The ability of a veterinarian or pharmacist to compound animal preparations from approved product is clearly described and permitted by federal law. This type of legal compounding is not addressed in Guidance #256 – there is nothing in the guidance to limit this practice in any way.

In addition, veterinarians sometimes need a drug containing an active pharmaceutical ingredient not found in an approved product. Guidance #256 clarifies important steps that veterinarians should take when requesting a patient-specific prescription be compounded from bulk drug substances. This does not change the law, but better protects the veterinarian by clarifying the process.

It is illegal to manufacture a drug from bulk substances without federal approval. Both state and federal laws ban the dispensing of illegal drugs.

If a conflict between federal and state law were to arise, the doctrine of preemption states the higher authority of law will displace the law of the lower authority of when they come into conflict.¹ The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives authority to the FDA to oversee the safety of drugs. Compounding of animal drugs from bulk drug substances results in new animal drugs that must comply with the FD&C Act's approval/ indexing requirements. This fact has been upheld by every Federal Court of Appeals that has considered the issue.

Claim: Compounding from bulk provides better quality than using FDA-approved products.

Logic, experience and published studies contradict this claim.

FDA-approved products have been proven to be safe and effective by data submitted to the agency. Bulk drug substances, typically imported from foreign countries, have not been subject to such scrutiny.

Makers of FDA-approved products must demonstrate the ability to manufacturer a safe product. Compounders have no such requirements. In the past ten years there have been at least three instances where errors made in the preparation of animal compounds have killed or led to the humane destruction of horses in multiple states.

Studies have shown differences in potency of the active ingredient in formulations/products from veterinary compound pharmacies.^{2,3} This can have serious consequences and impact the efficacy or toxicity of a product resulting in potential devastating results for the patient for which it is prescribed and administered.

Additionally, the bioavailability⁴ of compounded products is not evaluated. Therefore, it is difficult to determine if a compounded product is bioequivalent⁵ to the intended therapy. For example, a 2014 study evaluating bioequivalence of compounded itraconazole formulations found the compounded product produced such low plasma concentrations that it was unlikely to be effective.⁶

Claim: GFI #256 would give FDA new authority over veterinarians and pharmacies that provide compounded preparations.

The authority to regulate unapproved drugs is not new. Under the Food, Drug and Cosmetic Act, the manufacturing and sale of an unapproved animal drug is illegal. Compounding an animal drug from bulk substances makes it a new animal drug. This means that at present, a veterinarian or pharmacist who makes or dispenses a product compounded from bulk is selling an illegal drug. AHI believes this draft guidance strikes the correct balance between some compounding from bulk drug substances to meet medical needs while upholding the law and protecting patient safety.

Draft Guidance #256 provides recommendations to veterinarians and pharmacists to ensure proper records are kept and information communicated to the animal owner. Such records and communication are important to protect the veterinarian or pharmacist by instructing them on how to properly record the information needed to confirm federal enforcement is not needed.

Claim: FDA is adding new responsibilities to veterinarians.

Drugs should not be compounded without the involvement of a licensed veterinarian. Currently, compounders who manufacture products from bulk drug substances are doing so without veterinarians' instruction and acting as unregulated animal drug manufacturers. This practice is illegal.

AHI supports the FDA compromise position on the need for veterinary involvement. This may be from direct supervision (i.e. in-house compounding) or indirectly through a patient-specific request completed by a pharmacist in a state-licensed pharmacy or federal facility.

¹ <https://www.law.cornell.edu/wex/preemption>

² Stanley, Kynch, (2010) Comparison of Pharmaceutical Equivalence of Compounded Preparation for Pergolide Mesylate.

³ McConkey, Walker, Adams, (2012) Compounding errors in 2 dogs receiving anticonvulsants

⁴ Bioavailability is a measure of the rate or extent to which a therapeutically active chemical is absorbed from a drug product into the systemic circulation and become available at the intended site of action.

⁵ Two drugs are bioequivalent if there is no clinically significant difference in their bioavailability.

⁶ Mawby, et al (2014) Bioequivalence of Orally Administered Generic, Compounded, and Innovator-Formulated Itraconazole in Healthy Dogs

Claim: Implementation of GFI #256 will have serious and damaging ramifications on veterinary practice and patients.

Implementation of GFI #256 will improve veterinary practice and patient safety by raising the standard for compounded medication. It will provide more information and transparency to pet owners regarding the medications prescribed for their animals.

Animal owners expect that the medicines they give are safe and effective. Veterinarians make their treatment recommendation on scientific data. Products compounded by bulk have not been tested for quality, safety or efficacy. Therefore, there is a higher risk and history has shown this risk can carry deadline consequences.

Claim: Implementing GFI #256 would increase the cost of compounding by 300 percent.

Compounding currently permitted by federal law is unaffected by this guidance, and the cost and availability of this type of compounding should remain unchanged as well. Such price differences should only occur in those circumstances where compounders are currently acting like manufacturers and producing copies or near copies of approved drugs and selling them as cheaper alternatives.

Claim: The positive list of bulk drug substances that can be used to make products for office use is limited to only seven items, severely restricting veterinary care.

The guidance document establishes an initial list and sets up a process whereby anyone can nominate additional substances to be placed on the list. Veterinarians, pharmacies or anyone else may nominate bulk drug substances to be added to the list and provide information supporting the need for the substance.

Claim: Implementation of GFI #256 would eliminate access to compounded products in the case of a drug shortage.

The animal health industry is committed to working with FDA to identify root causes and offer recommendations to help prevent and mitigate true drug shortages. Efforts such as the FDA's recent report, "Drug Shortages: Root Causes and Potential Solutions" are an important step forward.

It is important the definitions of a drug shortage involve the availability, not desired cost, of a product.

Claim: GFI #256 mandates that compounding begin with FDA-approved drugs—this is not a requirement in human health.

GFI #256 specifically describes the circumstances under which animal preparations can be made from bulk drug substances. It does not mandate compounding only from FDA-approved drugs. The guidance states that a veterinarian can request a patient-specific prescription that is compounded from bulk drug substances if an FDA approved product is not available. The pharmacist can compound the drug from a bulk drug substance and dispense it, upon receiving the prescription, to the veterinarian or to the patient's owner or caretaker.

GFI #256 also creates a positive list of drugs for office stock. Office stock are drugs compounded by a veterinarian or pharmacist and sold to a veterinarian without a patient-specific prescription. The guidance actually describes the limited circumstances under which compounding from bulk substances – which is otherwise illegal – will be permitted by enforcement discretion to meet the medical needs of animal patients.

Would the following practices valued by veterinarians still be allowed under the new guidance?

Turn select oral medications into a topical treatment that can be rubbed into the skin of your pet's ear for easier administration when there is no topically administered approved drug.	✓ Yes
Add flavors to make medications more appealing.	✓ Yes
Turn pills into flavored solutions or suspensions.	✓ Yes
Create medications that have been discontinued.	✓ Yes

Compounding permitted under the Animal Medicinal Drug Use Clarification Act of 1994 is unaffected by this guidance.

Guidance #256 allows compounding from bulk drug substances for non-food producing animals with a patient-specific prescription as long as the compounded preparation is not a copy of an approved product. It can be a copy or near copy of an approved product if the veterinarian can document a clinical difference.

Guidance #256 also allows for the compounding of preparations from bulk drug substances for office stock – without a patient specific prescription – if the bulk drug substance is on a list maintained by FDA. FDA has established a process for adding and removing substances on the list.