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The FAQs on Compounding

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a. What is Compounding?[i]

Compounding can be generally defined as the manipulation of a drug, beyond its originally labeled form, to meet the needs of a particular patient. Compounding can be legally performed by a veterinarian or by a pharmacist upon receipt of a veterinarian's prescription for a particular patient. Compounding can include the modification of an approved drug or the synthesis of drugs from bulk products (raw ingredients). The latter is admissible under 'limited implied permission' and is only legal when specific criteria are met. In practice, compounding is undertaken in a variety of different ways, some legal and some not. Common examples of compounding in veterinary medicine include:

- Mixing two injectable drugs into one syringe
- Creating an oral suspension from crushed tablets
- Mixing two solutions together (ex. to instill into ears)
- Creating a transdermal gel
- Adding flavoring or formulating flavored medicated treats

b. Why Use Compounded Drugs?[ii]

The multitude of species treated in veterinary medicine and species-differences in pharmacodynamics, body size, and temperament necessitates the customized approach to patient care afforded by compounded drugs. Drug shortages, the paucity of FDA-approved treatment options, and issues in successful administration of drugs (client compliance) can mean compounded drugs are the only option for some veterinary patients. Changes in the concentration or dosage form can be critical to therapeutic success simply because it ensures better client compliance in administering the medication. Even the most seasoned feline practitioner has encountered an impossible-to-pill cat, and for these patients and their owners, transdermal gels or flavored treats are the only option. In addition to the substantial need for compounding in general, the AVMA also identifies certain specialties, such as wildlife rehabilitation, zoo animal medicine, and aquaria, that rely upon compounding from bulk ingredients to some degree.[iii]

c. Terminology: Bulk Drugs, Mimic Drugs, and Compounded vs. Generic Drugs

Bulk Drugs:

Bulk drugs are the chemical ingredients used to make the FDA-approved drug (the finished product). These ingredients can be raw drugs, active pharmaceutical ingredients (APIs), or pure chemicals. Bulk ingredients are not themselves FDA-approved and, like any compounded drug, the final product has not been evaluated for clinical efficacy and safety. Compounding from bulk products is generally prohibited, although exceptions exist in veterinary medicine under specific criteria (limited implied permission).[iv]

Mimic Drugs:

Mimic drugs are compounded drugs that copy an available FDA-approved human or animal drug. They are usually produced for economic (rather than medical) reasons because they avoid drug approval processes and have lower production costs. Mimic drugs may appear identical to the FDA-approved product but differ in safety and efficacy. The use of mimic drugs is illegal and unnecessarily exposes patients to substances not proven to be safe or effective. Their use by veterinarians undermines incentives for pharmaceutical development and marketing of animal drugs and could lead to fewer available treatment options.[v]

Compounded ≠ Generic:

Compounded drugs should never be thought of as interchangeable with generic drugs. A generic drug is a bio-equivalent to a brand-name drug in all the following: dosage form, efficacy, safety, strength, route of administration, quality, and intended use. Generics have the same ingredients and modes of action as the brand name version. They are not adulterated and do not contain inactive ingredients that alter pharmacokinetics. Unlike compounded drugs, generics must demonstrate bioequivalence of safety and efficacy with the pioneer drug product and are FDA-approved (indicated by ANADA numbers).[vi]

d. Drug Laws & Regulations

The use of therapeutic drugs in veterinary medicine is governed by several federal agencies, including the FDA, EPA, and USDA. The FDA regulates drug use via the Federal Food, Drug, & Cosmetic Act (FFDCA), the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), Extralabel Drug Use (ELDU) Rules, and the FDA's Compliance Policy Guide (CPG). The FDA enforces the FFDCA and its 'Good Manufacturing Practices', ensuring the safety and efficacy of drugs, devices, and the food supply. It is the governing body responsible for human and animal drug approval processes and regulation of animal foods, veterinary drugs, and medicated animal feeds. Federal over-sight is shared with the states via State Veterinary Practice Acts and Veterinary Medical Boards. The states define specific criteria for appropriate prescribing and dispensing of drugs, such as the veterinary-patient-client-relationship (VPCR).[vii]

Compounded drugs are regulated on both state and federal levels. The FDA defers day-to-day regulation to the states via State Medical Boards and State Boards of Pharmacy, which license and oversee pharmacies. Pharmacies are subject to the US Pharmacopeial Convention (USP) and State Pharmacy Acts. Compounding pharmacies, like traditional pharmacies, must be licensed and meet state-specific criteria to operate and sell products legally. The legal use of compounded drugs in veterinary medicine is defined by the FFDCA, AMDUCA, a subpart of the Extralabel Drug Use (ELDU) Rules, and the FDA's Compliance Policy Guide (CPG).[viii]

Compounding can be categorized in three ways: 1) Traditional Compounding; 2) Limited Implied Permission Compounding; and 3) Illegal Compounding. It is important to remember that compounding, regardless of the type, produces an unapproved new drug for which safety and efficacy have not been demonstrated.

1) Traditional Compounding[ix]

Traditional compounding involves the modification and extra-label use of an FDA-approved animal or human drug. Examples of traditional compounding include combining two FDA-approved injectable drugs into one syringe or formulating a transdermal gel from an FDA-approved tablet. An important criteria of traditional compounding is the use of an approved drug, which affords a more straightforward understanding of its legality. Both the Food, Drug, and Cosmetic Act and AMDUCA generally prohibit compounding from active pharmaceutical

ingredients (bulk drugs), but the FDA allows for exemptions in veterinary medicine and some bulk drug compounding can be conducted legally. However, the FDA's enforcement discretion has been criticized by the AVMA as being vague and lacking specificity.[x] Therefore, to mitigate risk, the most conservative way to engage in compounding would be to do so only in the form of traditional compounding (only from FDA-approved drugs).

Criteria for Legal Compounding:[xi]

- Comply with Federal and State Laws governing compounding & extralabel use
- Prescribe/compound on the basis of an established VPCR
- Prescribe/compound only in the absence of an FDA-approved drug and be able to demonstrate that failure to treat would result in harm to the patient
- Prescribe/compound commensurate to a specific patient's need and minimize compounding in advance of expected need
- Compounding must be performed by a licensed veterinarian or pharmacist

Food Animals:[xii]

Rules governing food animals and compounded drugs are very strict. Use of compounded drugs should be reserved for only exceptional circumstances and where implications for human safety are well known. In addition to the above criteria for legal compounding, examples of requirements for compounded drug use in food animals include:

- Perform adequate record-keeping and observe appropriate withdrawal times
- Abstain from use of substances that pose a public health risk
- Abstain from use of substances on the FDA's prohibited drugs list (for food animals)

2) Limited Implied Permission Compounding (from Bulk Drugs)[xiii]

Although the FFDCA and AMDUCA technically prohibit compounding from bulk drugs, the FDA recognizes that veterinary practitioners operate under circumstances sometimes necessitating the use of bulk drugs in compounding. In its enforcement discretion, the FDA acknowledges the unique requirements of treating a multitude of species, alongside the scarcity of approved drugs available to meet species-specific needs. As such, the FDA allows for compounding from bulk drugs but only in limited circumstances. Specific criteria must be met, alongside the requirements of traditional compounding.

Criteria for legal compounding from bulk drugs:

- If shown that the only treatment option is a drug compounded from bulk drugs;
- Must be able to demonstrate that an approved drug is not commercially available;
- Must be able to demonstrate that the needed compounded preparation cannot be formulated from an approved drug(s);
- Note – the FDA publishes a list of bulk substances for which it would likely observe enforcement discretion (ex. antidotes)[xiv]

3) Illegal Compounding[xv]

It is illegal to engage in the whole-sale manufacture of large quantities of compounded drugs using commercial-scale equipment, under the guise of traditional compounding. The compounding and use of 'mimic drugs', produced for economic gain and intended to copy available FDA-approved drugs, is illegal in all circumstances. Prescribing or producing large quantities of compounded drugs for stock-piling or resale to other veterinarians or pet owners is illegal. Depending on the state, keeping an inventory of compounded drugs based on historical need or compounding/prescribing any quantity of drug not commensurate to a specific patient's need is illegal. Some states also consider the sale/distribution of any quantity of compounded drugs to pet owners (out-patient use) to be illegal and only allow for in-patient use.

Common Problem Areas (examples warranting FDA enforcement action):[xvi]

- Compounding or prescribing compounded drugs even though an FDA-approved treatment option is available;
- Using mimic drugs that intentionally copy an FDA-approved product, either unknowingly or to save money;
- Preparing or stock-piling large quantities of compounded drugs for wholesale distribution or resale to other veterinarians or pet owners;
- Compounding from bulk ingredients in circumstances that fail to meet the FDA's enforcement discretion criteria