



Compounding Guide for the Food Animal Veterinarian

What is Compounding?

Compounding is the term used for combining, mixing, or altering ingredients to create a medication tailored to the needs of an individual patient.¹ It involves making a new drug for which safety and efficacy have not been demonstrated with the kind of data that FDA requires to approve a new drug. In virtually all cases, FDA regards compounded medications as unapproved new drugs.²

Using compounded medications is considered to be extralabel drug use (ELDU) of an approved animal or human drug. ELDU is possible under the Animal Medicinal Drug Use Clarification Act (AMDUCA).

When may a veterinarian consider using a compounded product in a food animal?

When there is no approved new animal or approved new human drug that, when used as labeled or in conformity with criteria established in this part, will, in the available dosage form and concentration, appropriately treat the condition diagnosed. [21CFR530.13].

The veterinarian must also ascertain that there is sufficient data to establish a withdrawal interval. This is the legal responsibility of the veterinarian and it is particularly important if a pharmacy is doing the compounding as they may not be aware of all the legal ramifications. If there is not sufficient data, then the veterinarian must assure that the animal and its products never enter the food chain.

Overall, compounding for food animals should be rare. When treating an animal whose tissues or products have the potential to enter the human food chain, it's important to remember that Food Safety and Public Health come first.

What are the requirements for legal use of a compounded product in food animals? [21CFR530.13]

1. All requirements for ELDU under AMDUCA are met
2. Additional stipulations specific for compounding:
 - a. An approved animal drug should be used for compounding before using an FDA approved human drug
 - b. Compounding is done by the veterinarian or pharmacist within their scope of practice

¹ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm208983.htm>

² <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm204237.htm>

- c. Adequate procedures are followed to ensure the safety and effectiveness of the compounded product
- d. Scale of compounding is in line with the need for the product and is for a particular patient. Compounding in anticipation of receiving prescriptions, except in limited quantities, is illegal. The compounding of large quantities can fall under “manufacturing” and thus the compounded product would be considered a drug in need of FDA approval. Also, compounding for third parties to resell or selling it at wholesale to another individual or entity for resale is illegal. So, it would not be legal for a compounding pharmacy to make a product for a veterinarian to sell to clients, for example, keep on his truck to sell to dairies. Products can be compounded “for office use.” This means that the drug is to be administered or applied in the prescriber’s office and if dispensed, only a limited supply, generally defined as up to a 72 hour supply, of the drug is to be given to the client. However, state laws may vary, check with your state board.
- e. All state laws relating to compounding are followed.

Compounding falls under AMDUCA, so what are the requirements for ELDU and Compounded Medications under AMDUCA?

a. Therapeutic Purpose

ELDU can only occur for therapeutic purposes when an animal’s health is suffering or threatened. This means that it is not covered by AMDUCA for reproductive purposes, growth promotion and efficiency, or research (with animals entering the food chain). Use for prophylaxis is a gray area and would require good documentation of ELDU being necessary.

b. No Effective Labeled Drugs

ELDU should not occur unless FDA approved drugs as labeled are clinically ineffective for their intended use.

c. VCPR

A valid veterinarian-client-patient relationship (VCPR) must exist

d. Veterinarian’s Supervision

ELDU is permitted only under the supervision of a veterinarian. So if a producer gives a drug, including Over the Counter (OTC) products, extralabel, then calls a veterinarian for a withdrawal interval, this is illegal. If the veterinarian gives a withdrawal interval recommendation (which must be documented in the records), he is assuming responsibility for the ELDU and can be held responsible, along with the producer, if there are any residues.

Any OTC product that is compounded in veterinary medicine is now deemed a prescription drug and may only be used under veterinarian supervision. This again is for the safety of the food chain.

e. Approved Drugs

ELDU is permitted using only FDA approved animal and human drugs. Medications approved for other food animal species should be used before using medications approved only for non-food animal species. Medications approved for animals

should be used preferentially over drugs approved for humans only. Using bulk chemical is not allowed as they are not FDA approved.

1. What are bulk chemicals? Defined in 21 CFR 207.3 “Bulk drug substance means any substance that is represented for use in a drug and that, when used in the manufacturing, processing, or packaging of a drug, becomes an active ingredient or a finished dosage form of the drug, but the term does not include intermediates used in the synthesis of such substances.” In other words, it is the drug in powdered chemical form, often used for research purposes and may not be of pharmaceutical grade.
2. Compounding with bulk chemical can be less expensive than using an FDA approved medication.
 - a. ELDU is legal for therapeutic purposes only in food producing animals, thus, cost is not an acceptable reason for ELDU under AMDUCA.
3. This bulk chemical is often manufactured in foreign countries with potentially less oversight than there is in the United States. As only a portion of states require a drug pedigree or a certificate of origin, there is no assurance that the product is safe and unadulterated and not a potential contamination to our food supply.

Bulk chemical exceptions: Antidotes that are not commercially available are the exception. Since FDA approved antidotes are not available on the market, the FDA has stated that in most circumstances, they will likely not pursue regulatory enforcement if food producing animals are treated with these bulk chemicals. It is recommended that for these exceptions, that only chemical made in facilities that meet USP standards and are licensed by the FDA be used. These exceptions include

1. ammonium molybdate
2. ammonium tetrathiomolybdate
3. ferric ferrocyanide
4. methylene blue (180 day meat and milk withdrawal)
5. picrotoxin
6. pilocarpine
7. sodium nitrite
8. sodium thiosulfate
9. tannic acid

f. Not in Feed

Extra-label use of an approved animal drug or human drug or feed additive in or on an animal feed is prohibited. Also, using combinations of medicated feed or feed additives not approved to be used together is considered illegal. ELDU in water is permitted.

Exceptions: CPG Sec 615.115 Extra-Label Use of Medicated Feeds for Minor Species specifies that regulatory action will not be taken in some instances of ELDU of medicated feed in minor species. The requirements to use feed ELDU in minor species are similar to the requirements for ELDU of medications. Some of the differences include:

- a. A written recommendation that includes the medical rationale, dated within 3 months prior to use is required. The producer and vet must keep copies that are available for FDA inspection.
- b. The medicated feed is approved in a major food producing species and is to be used in a food producing minor species.
- c. ELDU of medicated feed in aquaculture is limited to medicated feeds approved for use in aquatic species.

Refer to the FDA's Compliance Policy Guide on the extra-label use of medicated feeds for minor species, available at:

<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/UCM074659>

Additional clarifications may be found at:

<http://www.fda.gov/animalveterinary/newsevents/cvmupdates/ucm048037.htm>

g. Prohibited Drugs

ELDU is prohibited in food producing animals with the following drugs:

1. Chloramphenicol
2. Clenbuterol
3. Diethylstilbestrol (DES)
4. Nitroimidazoles such as metronidazole
5. Nitrofurans- including topical applications
6. Sulfonamides in adult lactating dairy cattle
7. Fluoroquinolones such as enrofloxacin can be used on label only
8. Glycopeptides such as vancomycin
9. Dipyrone
10. Gentian Violet
11. Phenylbutazone in adult dairy cattle (defined by the FDA as dairy cattle 20 months of age or older regardless of whether they are milking or dry)
12. Antiviral medications including adamantane and neuramidase inhibitors in poultry
13. Beginning April 5th, 2012, cephalosporins, not including cephalixin, must be used on label in cattle, swine, chickens and turkeys. They may be used extralabel only to treat a disease indication not labeled. See <http://www.gpo.gov/fdsys/pkg/FR-2012-01-06/pdf/2012-35.pdf> for more details.

Please note that regulations related to the Pasteurized Milk Ordinance (PMO) also prohibit the presence of dimethyl sulfoxide (DMSO) and colloidal silver on dairies.

h. No Residues: ELDU must not result in residues

i. Additional Food Animal Requirements:

1. Make a careful diagnosis and evaluation of the conditions for which the drug is to be used.
2. Establish a substantially extended withdrawal period supported by scientific information, if applicable. Unfortunately, the variability in the chemical make-up of compounded products and lack of pharmacokinetic data makes this difficult. This again is the main reason not to compound as we do not have the data necessary to keep the food supply safe.
3. Institute procedures to assure that the identity of the treated animal or animals is carefully maintained. If the individual animal cannot be identified for the extended withdrawal time, then the extended withdrawal time must be applied to the entire group.
4. Take appropriate measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food-producing animal subjected to extralabel treatment.

What needs to be in the records for ELDU and Compounded products?

1. Identify the animals, either as individuals or a group
2. Animal species treated.
3. Numbers of animals treated.
4. Conditions being treated.
5. The established name of the drug and active ingredient.
6. Dosage prescribed or used.
7. Duration of treatment.
8. Specified withdrawal, withholding, or discard time(s), if applicable, for meat, milk, eggs, or animal-derived food.
9. Keep records for 2 years.
10. FDA may have access to these records to estimate risk to public health.

What information should be on the prescription label?

1. Name and address of the prescribing veterinarian.
2. Established name of the drug.
3. Any specified directions for use including the class/species or identification of the animal or herd, flock, pen, lot, or other group; the dosage frequency, and route of administration; and the duration of therapy.
4. Any cautionary statements.
5. The veterinarian's specified withdrawal, withholding, or discard time for meat, milk, eggs, or any other food.

Commonly Asked Questions:

What is FARAD's stance on compounding in food producing animals?

FARAD discourages the use of compounded medications in food producing animals. Compounded drugs do not undergo the same quality assurance testing as commercially manufactured medications. In addition to this, there is a lack of pharmacokinetic data on compounded medications making a scientifically based withdrawal interval impossible to calculate.

Can a product be compounded for use on Dairy X?

No, products can only be compounded for an individual patient with whom the veterinarian has a valid VCPR. They should not be compounded for general use such as mastitis cases on the farm. The farm is not considered an individual patient.

How do I choose a compounding pharmacy?

This topic is covered in detail in the AVMA's brochure on veterinary compounding. It is available at:

<https://ebusiness.avma.org/EBusiness50/ProductCatalog/product.aspx?ID=155>

Where can I get more information on Compounding?

The AVMA has published a brochure on veterinary compounding available at:

<https://ebusiness.avma.org/EBusiness50/ProductCatalog/product.aspx?ID=155>

The FDA's Compliance Policy Guide for Compounding of Drugs for Use in Animals may be found at:

<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm074656.htm>

More details of the published law on compounding and AMDUCA may be found at:

http://farad.org/amduca/amduca_law.asp

The Society of Veterinary Hospital Pharmacists' statement on animal compounding, which includes helpful information for pharmacists and veterinarians, may be found at: www.svhp.org

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