Extralabel drug use in cattle with case examples

Virginia R. Fajt, DVM, PhD, DACVCP

College of Veterinary Medicine & Biomedical Sciences, Texas A&M University
College Station, TX 77843

Abstract

Cattle veterinarians have the responsibility of selecting, using, dispensing and prescribing drugs in a legal manner. The process for drug approval for food animals in the U.S. is briefly reviewed, and the federal law allowing extralabel drug use is detailed. Application of regulations to exemplar case scenarios are presented for illustration and discussion.

Disclaimer

I am not a lawyer and have not been employed by regulatory agencies; therefore, the following information is my interpretation only. Legal representation should be sought, or the relevant laws and regulations should be reviewed, if additional clarification is required.

Background for making legal drug selection and use decisions

Veterinarians have the privilege of drug prescribing as part of the practice of veterinary medicine and therefore the responsibility and obligation to use, dispense, or prescribe drugs in a legal manner. Navigating local, state and federal laws that touch on those responsibilities can be challenging, and the goal of this presentation is to share important rules and laws in the United States and the application of those rules and laws to case scenarios.

Definition of a drug

To set the stage for discussions about drug use, federal law defines what and how drugs can be sold via interstate commerce in the Federal Food Drug and Cosmetic Act (FFDCA), the Virus Toxins and Serums Act, and the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). A drug is defined in 21 U.S. Code 321 (in the FFDCA) as follow:

> "(g)(1) The term "drug" means (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C)."

Relevant federal agencies

Most veterinary drugs are under the jurisdiction of the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM), and in addition, if they fall into the categories of controlled substances, can be regulated by the Drug Enforcement Administration (DEA). Human drugs are also under the jurisdiction of FDA but a different center, the Center for Drug Evaluation and Research (CDER). The exceptions to drugs being approved by the FDA CVM are (1) drugs that fall under the U.S. Department of Agriculture (USDA) due to their nature as biological products (9 CFR 101) "…which are intended for use in the treatment of animals and which act primarily through the direct stimulation, supplementation, enhancement, or modulation of the immune system or immune response," and (2) drugs that fall under the Environmental Protection Agency (EPA) because they are pesticides and therefore regulated by FIFRA (7 U.S. Code 136).

There is no federal regulation of dietary supplements or nutraceuticals intended for animals. These products have no oversight as to product safety or efficacy. As long as the manufacturer of a supplement does not make a drug claim, there is very little regulators can do to control the sale of the supplement. However, if a manufacturer makes a claim on a website, in promotional materials, or on the label, they are at risk of a warning from the FDA CVM and could be ordered to stop production and sale of such a product, since it is an unapproved drug (see previous definition of a drug: if you intend to use the product as a drug, it is a drug, and drugs that are not approved are in violation of federal law).

Human supplements differ from supplements intended for animals; they fall under the Dietary Supplement and Health Education Act, which only prevents manufacturers from marketing products that are adulterated or misbranded, for example, if they make drug claims. Dietary supplements intended for humans are not required to demonstrate efficacy.

Drug approval

Drugs are approved by the FDA CVM in a standardized manner in order to demonstrate safety and efficacy for the intended use. Phases of drug approval include a preclinical phase, in which novel compounds are evaluated for therapeutic effects and for toxicity in vitro and in laboratory animals; Phase 1, in which a small number of healthy animals are administered the drug to evaluate safety and drug disposition; Phase 2, in which a small number of animals with the target condition are administered the drug to evaluate safety and efficacy; and Phase 3, in which a large number of animals with the target condition and in their natural environment, e.g., in production settings or private veterinary practices, are administered the drug in its final formulation to evaluate safety (target animal and human) and efficacy. In addition to studies that demonstrate safety and efficacy, drug sponsors must also submit the manufacturing plan and all of the labeling materials, including the insert, packaging and Freedom of Information Summary. Sponsors also must evaluate environmental impact of the drug.

Categories of veterinary drug approvals include approved, conditionally approved and indexed. Approved drugs can be marketed, and they can also be used in an extralabel manner, under certain circumstances (see below). Conditionally approved drugs can be marketed while the sponsor is still demonstrating efficacy; these are generally drugs for minor uses or minor species, can only be sold for up to 5 years with annual renewal

before they must be either fully approved or no longer marketed. They cannot be used in an extralabel manner. These drugs have the designation "CA" and then a number, e.g., Fidoquel-CA1, a phenobarbital-containing product conditionally approved for seizure control in dogs. Indexed drugs have not demonstrated safety or efficacy, and this category is only for drugs in which performing studies is unlikely; food animal drugs are not eligible for indexing.

Marketing categories of drugs are over-the-counter (OTC), prescription (designated on human-labeled drugs as Rx), and veterinary feed directive (VFD). OTC drugs do not require a veterinarian's oversight, prescription drugs can only be sold under the direction of a veterinarian, and VFD drugs require a veterinarian's order to be sold or to be fed. It is important to note, however, that the OTC designation is only valid if the drug is being used as labeled. For example, human OTC drugs prescribed for animals require a prescription or a veterinarian's label (as described in extralabel drug use regulations; see below and other resources).

To summarize, veterinarians can be confident that drugs approved by the FDA CVM are effective for the indication on the label, that the target animal and human safety have been characterized, and that they are manufactured using standardized practices in inspected facilities. Drugs that have not gone through the approval process do not have this assurance; for example, compounded drugs have no standardized manufacturing and have not been assessed for safety or efficacy. This is why the first choice for drug selection is a drug approved for the condition of interest if one exists. This is the first step in the algorithm for extralabel use justification: there is no need for extralabel drug use if a labeled drug is available.

State laws related to drug selection and use

State laws define veterinary practice in their state practice acts. The American Association of Veterinary State Boards provides contact information for all state veterinary boards at **https://www.aavsb.org/public-resources/find-regulatory-board-information**. State law also governs how drugs can be sold and distributed via state pharmacy acts, which may differ across states.

Federal laws related to drug selection and use

Federal law allows veterinarians to use and prescribe drugs in animals in an extralabel manner under specific circumstances. This law was first passed in 1994 as the Animal Medicinal Drug Use Clarification Act (AMDUCA) and has been amended periodically since then. Extralabel is defined as anything not included on the label, so use in a different species of animal, by a different route of administration, at a different dose, at a different frequency, at a different duration, for a different indication, or anything else not on the label. Under AMDUCA, extralabel use is not permitted for non-therapeutic purposes (such as growth promotion or reproduction), by or on the order of a layperson, if it results in an unsafe or violative residue, or of feed additives. Extralabel use of specified drugs or drug groups are not permitted – these are laid out in 21 CFR 530.41 (**https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-530/subpart-E/section-530.41**).

The following hierarchy (also laid out in the AVMA algorithm at **https://zingtree.com/deploy/tree.php?z=embed&tree_id=673679905**) can help veterinarians identify when extralabel use might be permissible:

- If there is an FDA-approved product labeled for the animal species, indication, needed dosage form and concentration, that is clinically effective, use the labeled product.
- If there is no FDA-approved product as described above, extralabel use of a drug approved in food animals is the next best option, as long as it is not on the prohibited list, it is not for use in or on animal feed, and there is adequate information to establish an extended withdrawal time.
- If there is no FDA-approved product approved in a food animal species, a product approved for non-food animals or for humans may be used.

Regardless of the justification of extralabel use, an extended withdrawal time must be established, label and record requirements must be met, and animals must be identified. The Food Animal Residue Avoidance Databank is a resource for withdrawal time estimates, but the veterinarian is ultimately responsible for any residues that arise from extralabel use.

General categories of legality of drug use and selection

Legal

- Drugs used exactly as on the label (same species, same indication, same regimen – dose/route/frequency/duration)
- Extralabel use for therapeutic purposes, by or on the order of a licensed veterinarian with a VCPR, that does not cause a residue above a tolerance or is a threat to public health, and that include specific labeling, record-keeping, and disclosure to the client (in some jurisdictions)

Illegal but of low regulatory priority

- Use of a drug compounded from bulk in a non-food animal (see GFI 256)
- Use of a feed additive extralabel in a minor species (see CPG 615.115)
  - This guide states that veterinarians will not be prosecuted for using feed additive drugs extralabel as long as the provisions are followed. This document does not make these uses legal; it just identifies an area of low regulatory priority.

Unclear legality

- Extralabel use of a USDA-approved drug

Illegal

- Extralabel uses listed in 21 CFR 530.41 (e.g., drugs such as chloramphenicol and enrofloxacin in food animals)
- Extralabel use in or on animal feed (whether OTC or VFD)
- Extralabel use for production or non-therapeutic uses
- Use of a drug that is not approved, e.g., drug approved in another country, CBD used as a drug
- Extralabel use of an EPA-approved drug
- Use of a drug compounded from bulk in a food animal
- Some uses of controlled substances, e.g., with improper documentation or prescriptions
- Use of conditionally approved drugs extralabel
- Extralabel use directed by a layperson
- Extralabel use without a VCPR

Case scenarios to illustrate legal issues

The scenarios below or similar ones will be reviewed during the presentation and provide opportunities for pointing out various aspects of legal and illegal extralabel drug use. The interpretations of legality are the author's and could be modified by applicable laws and clinical settings.

- Trenbolone-containing implant for estrus suppression in heifers
  - Extralabel for a production use is illegal.
- Clenbuterol for growth promotion in steers
  - Extralabel use of clenbuterol in food animals is illegal
- Enrofloxacin for collibacillois in pigs
  - If used as labeled, would be legal.
- Enrofloxacin for collibacillosis in calves
  - Extralabel use of fluoroquinolones is illegal.
- Clenbuterol for asthma in cats
  - Extralabel use of clenbuterol is not illegal in non-food animals so this could be legal.
- Metronidazole capsules for coccidiosis in goats
  - Extralabel use of metronidazole in food animals is illegal.
- Horse-labeled ponazuril for coccidiosis in calves
  - Extralabel use when there is a labeled product that is effective is illegal.
- Compounded ponazuril for coccidiosis in lambs
  - Compounding from bulk drug is illegal.
- Chlortetracycline feed additive at 500 mg/head/day to control abortions in sheep
  - Extralabel use of feed additives is illegal, but this would be of low regulatory priority according to CPG 615.115.
- Acepromazine for the 4-H steer
  - Extralabel use for non-production purposes is illegal. In addition, not a legal issue, but show rules may be zero tolerance so use during the show may be disallowed.
- Itraconazole purchased in Mexico for dermatophytosis in cats
  - Drugs approved in other countries are illegal under the FFDCA.

Resources for additional information

AVMA Definitions of antimicrobial use for treatment, control, and prevention, **https://www.avma.org/resources-tools/avma-policies/avma-definitions-antimicrobial-use-treatment-control-and-prevention**

DailyMed database of drug labels, National Library of Medicine/National Institutes of Health, **https://dailymed.nlm.nih.gov/dailymed/**

Definition of biological products, 9 CFR 101, **https://www.ecfr.gov/current/title-9/chapter-I/subchapter-E/part-101**

FARAD (Food Animal Residue Avoidance Databank), **http://www.farad.org/**

FDA Center for Veterinary Medicine

- Database of Approved Drugs, Animal Drugs @ FDA, **https://animaldrugsatfda.fda.gov**
- Antimicrobial resistance resources, **https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance**
- Transition of over-the-counter medically important antimicrobials for animals to prescription status, **https://www.fda.gov/animal-veterinary/cvm-updates/fda-announces-transition-over-counter-medically-important-antimicrobials-animals-prescription-status**
- CPG Sec 615.115 Extralabel Use of Medicated Feeds for Minor Species, **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-615115-extralabel-use-medicated-feeds-minor-species**
- Guidance for Industry 256 - Compounding Animal Drugs from Bulk Drug Substances, **https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-256-compounding-animal-drugs-bulk-drug-substances**

"From an Idea to the Marketplace: The Journey of an Animal Drug through the Approval Process," **https://www.fda.gov/animal-veterinary/animal-health-literacy/idea-marketplace-journey-animal-drug-through-approval-process**

Tolerances for residues of new animal drugs in food, 21 CFR 556, **https://www.ecfr.gov/current/title-21/chapter-I/subchapter-E/part-556**