

Legal and illegal drug use in small ruminants

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Abstract

Some small ruminant species (sheep, goats, and cervids) are considered food animals by the U.S. federal government. Important laws and regulations that govern selection and use of drugs in these species include the FFDCA and AMDUCA, which outline the definition of a drug, the drug approval process, and extralabel use of drugs in animals. The critical components of these laws and regulations are outlined along with some potential use scenarios to aid in application to drug selection and use.

Key words: drug decision-making, extralabel drug use, compounding, drug regulations

Disclaimer

The author is not employed by any federal or state agency which enforces drug regulations. Therefore, the information provided should be interpreted as the author's opinion, and any questions regarding drug regulations should be referred to the appropriate government agency for clarification.

Choosing drugs for use in any species includes some variation of these questions: are they legal, are they safe, and are they effective? "Effective" means that a treatment effect of some kind has been demonstrated, i.e., that the drug has been shown to change the outcome in treated animals. "Safe" means that the adverse effect profile is known and that therapeutic benefits of the drug outweigh the potential for adverse effect. Providing characteristics that define whether a particular drug use is legal is the aim of this presentation. By outlining important laws and regulations that govern drug selection and use and sharing example scenarios, practitioners can make reasonable determinations about the legality of drug selection and use in small ruminants, with a focus on sheep, goats and cervids. It may be helpful to categorize potential drug uses as legal, illegal but of low regulatory priority, unclear as to legality, or illegal.

Federal laws and regulations related to drug use

One important federal law related to drug use in animals is the Federal Food Drug and Cosmetic Act, its amendments, and its promulgated regulations that govern the approval of drugs for sale in the U.S. Drugs for animals are approved by the Food and Drug Administration (FDA) Center for Veterinary Medicine (CVM) using a standardized process that evaluates efficacy, safety, and manufacturing.⁷ Drugs approved for human use are approved by the FDA Center for Drug Evaluation and Research in a similar manner. Using drugs approved for the intended use, intended regimen, and intended species is legal, and the FDA-CVM database of approved animal drugs is easily searched to determine what is approved.⁹ Another source of information is the database of labels of drugs approved in humans and animals.¹³

Using drugs in a manner not in conformity with the label, i.e., extralabel, can be legal and is governed at the federal level in the U.S. by the Animal Medicinal Drug Use Clarification Act (AMDUCA) and its regulations.⁸ Many state veterinary practice

acts have language about extralabel use, which is often similar to what is codified in AMDUCA and its regulations, so state rules should also be consulted when selecting and using drugs. Important criteria that define legal extralabel use include:

- May only occur when the health of the animal is threatened or suffering or death may result if the animal is not treated. Extralabel use is not permitted for production purposes, such as lactation induction.
 - Must include the presence of a valid veterinarian-client-patient relationship
 - Must be no labeled product for the specific indication in the animal species of interest, or the product is clinically ineffective
 - Must affix a label with the required parts as outlined in the regulations for AMDUCA
 - Must keep records of extralabel use and its reasons for at least 2 years
 - Must assign an extended meat or milk withdrawal time
- Illegal extralabel use would include use by a layperson, use in or on animal feed, or use resulting in a residue presenting a risk to public health or above an established safe level or tolerance. Drugs not provided legal protection for extralabel use under AMDUCA are those not approved in the U.S. and those approved by agencies other than the FDA. If a compound is used as a drug, that is with the intention to treat, control, prevent, diagnose or control a disease, and it is not approved as a drug, such use is illegal. This includes drugs compounded from raw or bulk drug, which use should be considered illegal in food animals.⁶ An important caveat to the prohibition of extralabel use in or on animals feeds is the compliance policy guide issued by the FDA in 2016, which outlines the circumstances under which illegal extralabel use of drugs in feed in minor species will be overlooked or of low regulatory priority.⁴ This policy does not make the use legal, but it provides guidance in how to use drugs in feed in a manner that is not likely to be penalized.

Extralabel use of the following drugs is also illegal: fluoroquinolones (e.g., enrofloxacin); glycopeptides (e.g., vancomycin); furazolidone; nitrofurazone; other nitrofurans; chloramphenicol; dimetridazole; ipronidazole; other nitroimidazoles (e.g., metronidazole); sulfonamide drugs in lactating dairy animals; clenbuterol; diethylstilbestrol; phenylbutazone in female dairy cattle >20 months; and cephalosporins (not including cephapirin) in cattle, swine, chickens, and turkeys for disease prevention purposes, at unapproved doses, frequencies, durations or routes of administration, or if the drug is not approved for that species and production class.³

AVMA has a helpful algorithm for determining legal and illegal extralabel uses,¹ which identifies the hierarchy for drug selection in food animals as follows:

- (1) a product approved for the condition being treated which is effective as labeled
- (2) a product approved for a food animal that may be used in an extralabel manner
- (3) a product approved in non-food animals or humans that may be used in an extralabel manner.

If no products exist that satisfy (1), (2) or (3), a compounded product may be permitted, and the compliance policy guide on compounding should be consulted.

Food animals are defined not according to the owner's intended use, but rather by the FDA and the USDA. An owner's assurance that an animal will not enter the food chain does not allow for the violation of regulations related to food producing animals. A relevant quote from FDA CVM Draft Guidance for Industry #61, Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species: "For purposes of determining the food- or nonfood-producing status of minor species, we intend to consider a minor animal species to be food-producing when some members of the species are bred, cultured, farmed, ranched, hunted, caught, trapped, or otherwise harvested for the purpose of having the animals or edible products derived from the animals commercially distributed for consumption by humans or food-producing animals in the United States. This applies to any intended use in a food-producing minor species."¹¹ Therefore, sheep, goats and cervids should be considered food animals.

If you anticipate extralabel use, FARAD should be contacted for the most up-to-date advice on meat and milk withdrawal times.² As scientific information about the disposition of drugs changes over time, and as the ability to detect drugs at harvest changes with increased sensitivity of testing methodologies, withdrawal times change over time. Therefore, do not assume that a withdrawal time estimate from FARAD is accurate indefinitely, and contact them regularly for updates. Commonly requested withdrawal times are available on FARAD's website, and they respond quickly to online or emailed requests. In 2018, they also published about extralabel use and provided withdrawal times for common drugs.¹²

Changes should be anticipated in the legality of antimicrobial drugs currently available over the counter to lay people. In 2018, FDA-CVM released their goals related to antimicrobial stewardship in veterinary settings, one of which is to bring all dosage forms of medically important antimicrobial drugs under the oversight of a licensed veterinarian.^{5,10} This means that injectable antimicrobials that are currently available for purchase by laypersons over the counter are slated to become prescription products, according to the FDA, within the next 2 years.

Application of these laws and regulations can be challenging, especially when a regulation is silent about a particular use or is difficult to interpret. Practice in applying to various scenarios may be helpful, so the following are provided for your consideration, with an interpretation of legality based solely on the author's understanding of regulations and regulatory priorities:

Most likely legal

- Ketoprofen for ovine respiratory disease
- Ceftiofur for treatment of wound infection in a ewe
- Tulathromycin for caseous lymphadenitis in sheep

Legal but discouraged

- Gentamicin (injectable) for respiratory disease in a kid
- Gentamicin (oral) for colibacillosis in a group of lambs
- Sulfachlorpyridazine for treatment of metritis in lactating does

Legality uncertain

- Tilmicosin for treatment of respiratory disease in dairy ewe
- Pediatric human-labeled trimethoprim-sulfa for *E. coli* in a neonate
- DMSO and clotrimazole combination topically for ringworm in club lambs

Illegal but of low regulatory priority

- Distilled water with baking soda and 50% dextrose for fluid therapy in neonatal lambs or kids
- Oxytetracycline feed additive at 10 mg/lb for Mycoplasma arthritis in goats

Illegal

- Metronidazole for Giardia in a lamb
- Iodophor-containing surgical scrub/DMSO for intrauterine infusion in a doe
- Intramammary aloe vera for treatment of mastitis in a lactating doe
- Intramammary colloidal silver for treatment of mastitis in a lactating doe
- Enrofloxacin for treatment of respiratory disease in ewe lamb
- Six growth promotant implants in a vasectomized ram for heat detection

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