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LABEL AND EXTRALABEL DRUG USE IN SMALL RUMINANTS

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The selection of drugs for use in small ruminants can be problematic in the United States because of the paucity of approved products (see Tables 1 and 2 for products that are approved and currently marketed for goats and sheep in the United States). To effectively treat sheep and goats, practitioners must often use or prescribe products that are labeled for other species. Sheep and goats are food animals, and therefore, the consideration of public health and food safety is equally as important as the health of the animal. There are a number of small ruminant practitioners who treat animals that are considered companion animals rather than food animals, and they might argue that the regulations do not apply; however, the veterinarian would do well to remember that "[p]ractitioners who have used a prohibited substance in a companion or pack animal that subsequently enters the food supply would be subject to enforcement actions under the Food, Drug, and Cosmetic Act."[16] All veterinarians treating small ruminants, whether food producing or companions, must be familiar with the laws and regulations governing drug use in food animals. It should be emphasized that information in this article represents the author's interpretation of the laws and regulations and should be viewed as a starting point only. Practitioners should avail themselves of resources provided by the Food and Drug Administration and other agencies as the ultimate authority on interpreting the laws and regulations regarding drug use (see the Appendix at the end of this article for contact information).

From the Veterinary Antimicrobial Decision Support System, Iowa State University College of Veterinary Medicine, Ames, Iowa

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LABELED DRUGS

Approval of New Animal Drugs

Drugs approved in the United States must be shown to be effective as well as safe and are approved for specific indications. A drug sponsor (e.g., a pharmaceutical company) is required to perform many studies on safety such as target animal, human food, user, and environmental safety. Studies must also be performed on effectiveness that may include controlled clinical trials, field investigations, in vitro studies, laboratory animal studies, or bioequivalence trials. The data package submitted to the Food and Drug Administration Center for Veterinary Medicine (FDA-CVM) is considered a new animal drug application (NADA), to which a unique number is assigned. Other information required for a NADA includes manufacturing controls, environmental assessment, and labeling information. The approved drug product or NADA includes the drug, the packaging, and the labeling.

The approval process for drugs for small ruminants may take a slightly different tack than for the major food animal species. By definition, *minor species* means animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats.[14] It may be possible to extrapolate data from major to minor species, particularly in the area of human food safety.[12] This can be particularly beneficial in the case of a drug already approved in a major species, for which human food, user, and environmental safety data have already been generated. If data are published in public master files (see "Minor Use Program" discussion in the following section), they may be referred to in a minor species drug application, or the sponsor may receive authorization to refer to another NADA for the purposes of data extrapolation.

In the past, sheep were considered major species for purposes of data collection on human food safety for NADAs; however, effective as of September 5, 2000, sheep are considered a minor species for all data-collection purposes for new animal drug approvals, allowing sponsors of NADAs to extrapolate human food safety data from a major species such as cattle to sheep.[15] This change allows the extrapolation of the tolerances for drug residues of new animal drugs in cattle to sheep. It is expected to lower research costs by lessening preapproval study requirements, and perhaps by encouraging submissions of NADAs for approval for sheep.

Minor Use Program (National Research Support Program-7)

Because generating data for the approval of new animal drugs is expensive, drugs for use in minor species are often not pursued by sponsors. The Minor Use Animal Drug Program was started by the US Department of Agriculture in 1982 to facilitate the approval of drugs for minor species and for minor uses in major species (originally part of another program, it became the National Research Support Program-7 in 1993). This program prioritizes animal drug requests for funding to collect data required by the FDA-CVM for drug approval, assists in the development of study protocols, and provides funding for research studies. The data generated are then published as public master files and can be referenced at no cost by sponsors such as pharmaceutical companies involved in NADAs. The program provides incentive for sponsors to submit applications for minor species and minor uses. Since the program began, 25 public master files covering 14 species and 16 drugs have been published, leading to FDA-CVM approval of, for example, ceftiofur for bacterial pneumonia in sheep and morantel tartrate for gastrointestinal parasites in goats.[17] Since 1998, data have become available as public master files for the following drugs: tilmicosin for bacterial pneumonia in sheep,[20] albendazole for liver flukes in goats,[1] amoxicillin for bacterial pneumonia in sheep,[2] and ceftiofur sodium for bacterial pneumonia in goats.[4]

Currently Approved Products

Tables 1 and 2 list the currently approved and marketed products for sheep and goats. As indicated in the tables, products are approved for an indication, in a species, for a route of administration, and at a dose, and any use other than that on the label is considered extralabel.

EXTRALABEL USE OF DRUGS

Animal Medicinal Drug Use Clarification Act of 1994

The Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) is one of the most significant pieces of legislation relating to drug prescribing by veterinarians because it legalized the practice of using drugs in a manner not described on the label, that is, extralabel. The regulations that promulgated AMDUCA became effective on December 9, 1996.[10] In particular, AMDUCA affects the small ruminant practitioner whose arsenal of labeled products is limited, as shown in Tables 1 and 2. Extralabel use may mean in a species, by a route, by a dose, at a frequency, or in any other manner not indicated on the label. The American Veterinary Medical Association published a flowchart in the January 1998 issue of the *Journal of the American Veterinary Medical Association* to assist the practitioner in making decisions about legal extralabel drug use (see the Appendix for web site and contact information). Although the regulations stemming from AMDUCA have been addressed in numerous professional publications, highlights of the regulations are provided here for review.

Table 1. DRUGS APPROVED FOR USE IN GOATS BY THE FOOD AND DRUG ADMINISTRATION CENTER FOR VETERINARY MEDICINE AND CURRENTLY MARKETED

Active Ingredient	Trade Name(s)	Type	Animal Type	Indication	Dosage
Decoquinate	Deccox	Feed additive	Young goats	Prevention of coccidiosis	0.5 mg/kg/d
Fenbendazole	Panacur	Oral	Goats	Treatment of *Haemonchus* and *Ostertagia*	5 mg/kg
Monensin	Rumensin	Feed additive	Confined-fed, nonlactating goats	Prevention of coccidiosis	20 g/ton
Morantel tartrate	Rumatel 88	Feed additive	Goats	Removal and control of mature gastrointestinal nematodes	0.44 g/100 lb
Neomycin	Biosol Liquid, Neomix, Neomycin, Neosol	Water medication	Goats	Treatment and control of colibacillosis caused by *Escherichia coli* susceptible to neomycin	10 mg/lb for a maximum of 14 days

Data from Compendium of Veterinary Products, ed 5. Port Huron, MI, North American Compendiums, 1999.

Table 2. DRUGS APPROVED FOR USE IN SHEEP BY THE FOOD AND DRUG ADMINISTRATION CENTER FOR VETERINARY MEDICINE AND CURRENTLY MARKETED

Active Ingredient	Trade Name(s)	Type	Animal Type	Indication	Dosage
Albendazole	Valbazen	Oral	Sheep	Treatment of nematodes	3 mL/100 lb
Ceftiofur sodium	Naxcel	Injectable	Sheep (may be used in lactating sheep)	Treatment of sheep respiratory disease associated with *Pasteurella haemolytica* and *Pasteurella multocida*	0.5–1.0 mg/lb
Chlortetracycline	Pennchlor Aureomycin	Feed additive	Breeding sheep	To reduce the incidence of abortion caused by *Campylobacter fetus* infection susceptible to chlortetracycline	80 mg/head/d
Decoquinate	Deccox	Feed additive	Young sheep	Prevention of coccidiosis	0.5 mg/kg/d
Ivermectin	Ivomec Sheep Drench	Sheep	Treatment of gastrointestinal roundworms	Lungworms and nasal bots	200 μg/kg
Lasalocid	Bovatec	Feed additive	Sheep in confinement	Prevention of coccidiosis	20–30 g/ton of total ration to provide 15–70 mg/head/d
Levamisole	Levasole Soluble Drench Powder, Tramisole Sheep Wormer Oblet, Tramisole Soluble Drench Powder, Prohibit	Sheep	Treatment of stomach worms	Intestinal worms and lungworms	1 bolus (0.814 g)/50 lb or 0.5 oz (11.7-g package in 1 quart)/50 lb
Neomycin	Biosol Liquid, Neomix, Neomycin, Neosol	Water medication	Sheep	Treatment and control of colibacillosis caused by *E. coli* susceptible to neomycin	10 mg/lb for a maximum of 14 days

Table continued on following page

Table 2. DRUGS APPROVED FOR USE IN SHEEP BY THE FOOD AND DRUG ADMINISTRATION CENTER FOR VETERINARY MEDICINE AND CURRENTLY MARKETED *(Continued)*

Active Ingredient	Trade Name(s)	Type	Animal Type	Indication	Dosage
Oxytetracycline	OXTC, Terramycin, Pennox	Feed additive	Nonlactating sheep	Treatment of bacterial enteritis caused by *E. coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline	10 mg/lb daily continuously for 7–14 days
Oxytocin	Several manufacturers	Injectable	Ewes	For obstetric use	30–50 IU
Penicillin G procaine	Agri-cillin	Injectable	Sheep	Treatment of disease organisms susceptible to penicillin	3000 IU/lb
Penicillin G procaine	Aquacillin Pen-G, Pen-G Procaine, Penicillin G Procaine, Penject, Crysticillin, Microcillin	Injectable	Sheep	Treatment of bacterial pneumonia caused by *Pasteurella multocida*	3000 IU/lb
Selenium/ tocopherol	BO-SE	Injectable	Lambs and ewes	Prevention and treatment of white-muscle disease	1 mL/40 lb in lambs, 2.5 mL/100 lb in ewes (1 mg/mL solution)

Data from Compendium of Veterinary Products, ed 5. Port Huron, MI, North American Compendiums, 1999.

Permitted Extralabel Uses

The provision for legal extralabel drug use is limited to therapeutic uses when the health of the animal is threatened or suffering or death may result if the animal is not treated. Extralabel use of drugs for production purposes is not permitted under these regulations; production drugs include drugs used for manipulation of reproduction or for growth promotion. Extralabel use under these regulations applies only to animal- or human-labeled drugs with NADA or new drug application (NDA) numbers; this has been interpreted to mean that these regulations do not apply to using unapproved drugs. Any compound for which the diagnosis, cure, treatment, mitigation, or prevention of a disease is claimed is considered a drug under the Federal Food, Drug, and Cosmetic Act, and if that product does not have a NADA or an NDA, it is considered adulterated or unapproved. So-called "natural products" might fall into this category if they are used as drugs; for example, intramammary plant extracts used to treat mastitis. Their origin is immaterial, but rather their intended use defines them; use of such products for treatment of disease would be considered a violation of the Federal Food, Drug, and Cosmetic Act.

Biologics or pesticides that are regulated by other agencies such as the Environmental Protection Agency (EPA) or the US Department of Agriculture are also not covered under AMDUCA. In fact, pesticides approved by the EPA carry a label that states that use of the product not in accordance with the label is a violation of federal law.

Drugs may be used in an extralabel manner in food animals under the following conditions:[10]

(a) If animal health is threatened or suffering or death may result from failure to treat.
(b) By or on the written or oral order of a licensed veterinarian in the context of a valid veterinarian-client-patient relationship (VCPR) defined as follows:
    1. A veterinarian has assumed the responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (the owner of the animal or animals or other caretaker) has agreed to follow the instructions of the veterinarian;
    2. There is sufficient knowledge of the animal(s) by the veterinarian to initiate at least a general or preliminary diagnosis of the medical condition of the animal(s); and
    3. The practicing veterinarian is readily available for follow-up in case of adverse reactions or failure of the regimen of therapy. Such a relationship can exist only when the veterinarian has recently seen and is personally acquainted with the keeping and care of the animal(s) by virtue of examination of the animal(s), and/or by medically appropriate and timely visits to the premises where the animal(s) are kept.

(c) If there is no approved product or the approved product is clinically ineffective as determined within a valid VCPR.
(d) After establishing a careful medical diagnosis and an extended withdrawal time, assuring the identity of treated animals is maintained, and assuring that the withdrawal time is observed and that no illegal residues occur.

Drugs that are labeled for non–food-producing animals or for humans are not required to undergo the same rigorous human food safety testing as food animal drugs. Therefore, scientific evidence may not be available on human food safety, or residue data may not be published that permit establishing a withdrawal time. In those cases, the drug may not be used. In addition, a drug labeled for non–food-producing animals or humans may not be used if a drug labeled for food animals can be used in an extralabel manner.

Records. When drugs are used in an extralabel manner, written records must be kept by the veterinarian for 2 years. The records are expected to contain the established name of the drug and its active ingredient, or if formulated from more than one ingredient, the established name of each ingredient; the condition treated; the species of the treated animal(s); the dosage administered; the duration of treatment; the numbers of animals treated; and the specified withdrawal, withholding, or discard time(s), if applicable, for meat, milk, eggs, or any food that might be derived from any food animals treated. These records are not for enforcement purposes, but rather to allow for the FDA to determine if any extralabel drug use presents a human health risk.

Labeling of Drugs by Veterinarians or Pharmacists. Extralabel drugs that are dispensed are required to have a label that includes the following:[10]

(a) The name and address of the prescribing veterinarian, or the name of the veterinarian and the name and address of the dispensing pharmacy;
(b) The established name of the drug or, if formulated from more than one active ingredient, the established name of each ingredient;
(c) Any directions for use specified by the veterinarian, including the class/species or identification of the animal or herd, flock, pen, lot, or other group of animals being treated, in which the drug is intended to be used; the dosage, frequency, and route of administration; and the duration of therapy;
(d) Any cautionary statements; and
(e) The veterinarian's specified withdrawal, withholding, or discard time for meat, milk, eggs, or any other food which might be derived from the treated animal or animals.

Illegal Extralabel Use

The following are *not* permitted under AMDUCA:[10]

(a) Extralabel use in an animal of an approved new animal drug or human drug by a lay person (except when under the supervision of a licensed veterinarian);
(b) Extralabel use of an approved new animal drug or human drug in or on an animal feed;
(c) Extralabel use resulting in any residue which may present a risk to the public health; and
(d) Extralabel use resulting in any residue above an established safe level, safe concentration, or tolerance.

As of this writing, drugs banned for use in food animals are chloramphenicol, clenbuterol, diethylstilbestrol, dimetridazole, ipranidazole, other nitroimidazoles such as metronidazole, sulfonamides in dairy cattle (except approved uses of sulfadimethoxine and two other sulfa drugs no longer being marketed), dipyrone, fluoroquinolones (except approved uses), glycopeptides, and extralabel use of medication in feed. Nitrofurans (nitrofurazone, furazolidone) are also banned, although there is currently an exemption for the approved topical uses of nitrofurans; however, because no products are currently marketed with a food animal label, in effect, all nitrofurans are banned. Studies have shown that residues can occur even with topical uses of nitrofurans, so it is likely that this exemption will be removed in the future.[16] Other drugs may be added at any time, so the veterinarian is urged to monitor the FDA for announcements.

As of April 1, 2000, the drugs for which a maximum allowable residue, that is, tolerance, has been established in sheep and goats are listed in Table 3. If a drug has no established tolerance, it is effectively zero, meaning that any residue is violative. The consequence of zero tolerance for nonapproved products is the requirement of extended withdrawal times when these products are used so that no residues are present in food products.

Establishing Extended Withdrawal Intervals

One provision of extralabel drug use is that extended withdrawal times must be provided by the veterinarian. At the time of this writing, the premiere source of withdrawal time information, the Food Animal Residue Avoidance Databank (FARAD), was in serious jeopardy because of a lack of funding. In the hopes that this has been remedied, it is recommended that withdrawal time information be obtained from FARAD (refer to the Appendix for contact information). FARAD has published a few withdrawal time estimates for small ruminants; they are listed in Table 4.

The methods used by FARAD to establish withdrawal interval estimates are varied. Withdrawal information for products that are labeled

Table 3. DRUGS FOR WHICH TOLERANCES HAVE BEEN ESTABLISHED AS CODIFIED IN THE CODE OF FEDERAL REGULATIONS, TITLE 21, PART 556*

Drug	Species
Albendazole	Sheep
Chlortetracycline	Sheep
Decoquinate	Goats
Estradiol	Lambs
Fenbendazole	Goats
Ivermectin	Sheep
Lasalocid	Sheep
Levamisole	Sheep
Monensin	Goats
Morantel tartrate	Goats
Neomycin	Sheep, goats
Oxytetracycline	Sheep
Penicillin†	Sheep
Tetracycline	Sheep
Thiabendazole	Sheep, goats
Zeranol‡	Sheep

*Revised as of April 1, 2000.
†Tolerance for penicillin is zero in uncooked edible tissues and milk.
‡No residues may be found in uncooked edible tissues by the detection method enumerated in the regulation.

Table 4. PUBLISHED SUGGESTED WITHDRAWAL INTERVALS AS ESTIMATED BY THE FOOD ANIMAL DRUG AVOIDANCE DATABANK

Drug	Species	Dose or Regimen	Meat Withdrawal Interval	Milk Withdrawal Interval
Acepromazine[7]	Sheep, goats	Up to 0.13 mg/kg IV; up to 0.44 mg/kg IM	7 days	48 hours
Aspirin[9]	Food animals	Typical uses	24 hours	24 hours
Detomidine[7]	Sheep, goats	Up to 0.08 mg/kg IM or IV	3 days	72 hours
DMSO[3]	Food animals	Not specified	4 days	96 hours
Ketamine[7]	Sheep, goats	Up to 2 mg/kg IV; up to 10 mg/kg IM	3 days	48 hours
Ketoprofen[9]	Sheep, goats	Up to 3.3 mg/kg, once a day, for up to 3 days	7 days	24 hours
Lidocaine with epinephrine[7]	Sheep, goats	Infiltration, epidural	1 day	24 hours
Oxytetracycline[13]	Small ruminants	6.6–11.0 mg/kg parenterally Multiple doses or high doses		Test milk after 96 hours Test milk after 144 hours
Xylazine[7]	Sheep, goats	0.016—0.1 mg/kg IV; 0.05–0.3 mg/kg IM	5 days	72 hours
Yohimbine[7]	Sheep, goats	Up to 0.3 mg/kg IV	7 days	72 hours

IV = intravenously; IM = intramuscularly.

in other countries for the proposed extralabel use may be extended.[8] Generally speaking, withdrawal times are established by most regulatory agencies, foreign or domestic, based on tissue depletion kinetics, using statistically derived data: the *withdrawal time* is defined as the time at which 99% of animals would be expected to reach the tolerance (or maximum residue level outside the United States). The tolerance or maximum residue level is based on food safety and food consumption factors. For products with no approvals, pharmacokinetic data are used to extrapolate when drug concentrations would be expected to reach nondetectable levels (or to reach the tolerance if one exists), then time is usually added to provide a greater safety margin.

Some rules of thumb may be used to extrapolate withdrawal times in the absence of data from FARAD when drugs are used in an extralabel manner:[18]

1. If a drug displays linear behavior, that is, if it is eliminated in a linear fashion (most drugs behave this way at pharmacologic doses), doubling the dose will, in essence, move the plasma concentration curve one half-life. Conceptually, this should be intuitive, because doubling the dose will double the initial concentration, and the time it takes to deplete half the concentration is defined as the *elimination half-life*.[19] Adding one half-life to the withdrawal interval should be sufficient, with the caveat of using the same route and volume per site as for the original dose.
2. It takes 10 half-lives to eliminate 99.9% of a drug; therefore, 10 half-lives may be a starting point for extrapolating a withdrawal time. Of course, certain limitations are inherent in this calculation: There must be no tissue depots that result in small but detectable drug levels in tissues (such as with aminoglycosides). The presence of 0.01% of the original dose must be nondetectable or below tolerance or safe level. The elimination behavior of the drug must be linear at the dose administered. Pharmacokinetic data may be found in the published literature, and abstracts available on web sites such as the National Library of Medicine may provide that information (see Appendix).
3. Half-lives of a given drug are generally shorter in smaller species. Because many of the drugs used by small ruminant practitioners are already approved in cattle, the withdrawal interval may be directly extrapolated from the cattle withdrawal time. It is prudent to add a period of time as a safety margin. Drugs can be metabolized differently in different species, but because the species in question are all ruminants, this is less likely.

It should be reiterated that AMDUCA specifically states that if scientific information regarding public safety and pharmacokinetic information are not available for a particular drug, the drug should be avoided completely or the practitioner must ensure that the animal never enters the food supply.

OTHER REGULATIONS REGARDING DRUG USE

For sheep or goat producers selling Grade A milk to the public, the Pasteurized Milk Ordinance is applicable to their operations.[11] The Pasteurized Milk Ordinance states that animal drugs and medications and equipment used to administer them shall be stored so as not to contaminate milk, milking equipment, wash vats, and hand sinks. Animal drugs and medications shall be properly labeled and segregated, lactating from nonlactating (separate shelves will suffice). Drugs shall be labeled with the name of the distributor (for over-the-counter drugs) or veterinarian (for prescription and extralabel drugs), directions for use, cautionary statements and active ingredient(s). Unapproved drugs shall not be used in dairy animals or stored in the milkhouse, milking barn, stable, or parlor.

The FDA publishes regulatory guidance materials for their field personnel known as *Compliance Policy Guides* (CPGs). These CPGs are designed to assist FDA personnel in enforcing current laws and regulations. There is a CPG manual available from the FDA, and the documents are also listed on its web site. There are a few CPGs that apply in particular to drug use in small ruminants and that should be mentioned here.

The first relates to compounding of drugs. The CPG on compounding (Section 608.400) defines *compounding* as "any manipulation to produce a dosage form drug other than that manipulation that is provided for in the directions for use on the labeling of the approved drug product, for example, the reconstitution of a sterile powder with sterile water for injection."[6] Compounding by definition results in an unapproved or adulterated drug. This guide states that although compounding is not legal under the Food, Drug, and Cosmetic Act, regulatory action will not be taken under certain circumstances, which include but are not limited to the following:

1. A legitimate medical need is identified (the health of animals is threatened and suffering or death would result from failure to treat the affected animals),
2. There is a need for an appropriate dosage regimen for the species, age, size, or medical condition of the patient, and
3. There is no marketed approved animal drug, when used as labeled or in an "extralabel" manner, or human-label drug, which may treat the condition diagnosed in the available dosage form, or there is some other rare extenuating circumstance.

The guide also gives explicit detail as to how the compounded product should be labeled and requires assurances regarding target animal safety and efficacy, human safety, withdrawal times, and expiration dates. The guide should be reviewed for the details of this information.

The guide also states that the following actions are among those for which there may be a high priority for regulatory action:

1. Compounding of bulk drugs for food animals except under special circumstances such as antidotes or large-volume electrolytes (FDA-CVM should be contacted for advice on what drugs fall into this category because they are subject to change)
2. The use of fanciful names, colorings, or other additives
3. Dispensing large quantities of compounded products
4. Occurrence of residues associated with compounded products
5. Compounded products not bearing required labeling

AMDUCA also addresses compounding: Compounding of *approved* drugs is permissible under the conditions stated in the previous discussion on AMDUCA if there is no approved drug that will, in the available dosage form and concentration, appropriately treat the condition diagnosed. This part of AMDUCA does not permit the compounding of unapproved products.

Another CPG that may affect small ruminant practitioners is not yet in effect. A draft CPG relating to the extralabel use of medicated feeds in minor species has been published but is not yet final (615.115, "Use of Medicated Feeds for Minor Species"). This CPG states that regulatory action is unlikely if feed additives are used in a minor species in a manner inconsistent with the label *if certain conditions are met*. Some of those conditions include the following:

1. Using the feed only with the expressed prior written recommendation (including the medical rationale such as diagnosis, drug selection, dose and duration, and the required withdrawal period dated within 3 months before use) and oversight of an attending licensed veterinarian within the context of a valid VCP relationship.
2. Limiting extralabel use of medicated feed to treatment modalities only so long as the health of an animal is threatened and suffering or death may result from failure to treat.
3. Reporting any adverse reaction within 10 days to the FDA.

It is important to remember that CPGs are *not* legally binding, but rather provide guidance for FDA personnel in enforcement actions. The FDA may decide at any point to revoke the CPG or not to follow its recommendations. This CPG concerning extralabel use of feed additives is still in draft form, and therefore is not yet in effect. Practitioners should monitor the FDA-CVM web site and other sources for additional information.

ISSUES FOR SPECIFIC DRUGS

The following is a discussion of selected commonly used types of drugs and the regulations potentially affecting their use. Again, it should be stated that the comments regarding the legality of various uses of drugs in small ruminants are the author's interpretation only, and the

veterinary practitioner is responsible for verifying their accuracy with the appropriate agencies.

Anesthetics and Sedatives

There are no approved currently marketed products in this group for small ruminants, with the exception of Metofane (methoxyfluorane). As discussed previously, the extralabel use of drugs is permitted only when animal health is threatened or suffering or death may result if not treated. Most uses of anesthetics and sedatives fall in this category; however, uses of sedative and like drugs for purposes of production or for events such as livestock shows would most likely be viewed by regulatory agencies as violating AMDUCA.

Anthelmintics

Demonstrated parasite resistance should be considered a legitimate rationale for extralabel use, whether increased dose or use of a different compound altogether. Parasiticides have been extensively studied as to pharmacokinetics and efficacy, and information should be readily available for withdrawal time estimation.

Antibiotics

Aminoglycosides

The use of aminoglycosides in ruminants has been the subject of debate for several years. Neomycin is labeled for cattle, sheep, and goats for colibacillosis; however, gentamicin is labeled only for horses and pigs, so there is no tolerance set for gentamicin in ruminants. Gentamicin has a terminal elimination phase such that a nontherapeutic but detectable concentration of drug may be present in the kidney if a prolonged withdrawal interval is not followed, in some cases up to 18 months for meat. AMDUCA regulations require that drugs may not be used in an extralabel manner if such use results in violative residues. Currently, several practitioner associations (American Veterinary Medical Association, American Association of Bovine Practitioners, Academy of Veterinary Consultants) have resolutions stating that the use of extralabel aminoglycosides should be avoided in cattle. The Executive Committee of the American Association of Small Ruminant Practitioners has also voted to endorse these resolutions. This does not mean that the use of gentamicin in sheep and goats is illegal; rather it is incumbent upon the veterinarian to make the decision regarding use and to set extended withdrawal times as necessary.

Fluoroquinolones

The fluoroquinolone antimicrobials approved in veterinary species in the United States include enrofloxacin, difloxacin, and sarafloxacin, to name a few. According to regulations promulgated under AMDUCA, the extralabel use of fluoroquinolones is *banned* in food animals, meaning that the small ruminant practitioner in the United States may not use *any* fluoroquinolones in sheep or goats, because none are labeled for small ruminants. The reason for the ban is the concern for increasing antimicrobial resistance in food-borne pathogens and the potential for resistance selection with the use of fluoroquinolones, which are considered first-line therapy for certain serious infections in humans. *The use of fluoroquinolones that violates this ban could potentially result in the withdrawal of all currently labeled fluoroquinolone products in food animals and jeopardize the future approval of new antimicrobials in food animals.*

Feed Additives

AMDUCA explicitly prohibits the extralabel use of drugs in or on feed, which presents a particular problem to large herds or flocks, because handling animals individually may not be an option for drug administration. For example, chlortetracycline is labeled for use in reducing the incidence of abortion due to *Campylobacter* at a dose of 80 mg/head/day, yet commonly used dosages are 300 to 500 mg/head/day. This practice is illegal according to AMDUCA; however, as discussed previously, there is a draft CPG that would allow the extralabel use of feed additives in minor species if certain conditions are met. Practitioners should monitor the FDA-CVM publications for further action on this draft CPG. This prohibition on the use of feed additives does *not* include drugs used in water. Drugs approved for use in water may be used in an extralabel manner under the conditions set forth in AMDUCA.

Hormones and Drugs Used to Manipulate Reproduction

Prostaglandins and other hormones are often used in small ruminant medicine for estrus synchronization, embryo transfer, and so forth. Because most of these products are not approved for use in sheep and goats, they are used in an extralabel manner. The practitioner should be aware that under AMDUCA, nontherapeutic extralabel use is not permitted, so regulatory guidance should be requested on the use of these products.

Miscellaneous Drugs

Dimethyl Sulfoxide

There are some jurisdictions in which dimethyl sulfoxide (DMSO) has been specifically prohibited; for example, in dairies, and this would supercede the federal regulations. Under federal regulations, the extralabel use of DMSO is permitted under the conditions addressed in

AMDUCA, if the product used extralabel is medical grade and therefore has a human drug approval and label. If the product is the technical-grade DMSO (which is usually cheaper), AMDUCA would not allow for its use, because it is not an approved new animal or human drug.

Various Antidotes

The use of antidotes for toxicities can be problematic in terms of regulations. For example, methylene blue and sodium thiomolybdate are not approved drugs and are usually produced at animal side from the bulk chemicals. This administration is a violation of AMDUCA, which only authorizes the extralabel use of approved new animal and human drugs. Under certain circumstances, however, the FDA may overlook such uses for the purposes of treating these conditions. The best advice for the practitioner is to seek advice from FDA personnel on the specific compound in question.

SUMMARY

The small ruminant practitioner has a small arsenal of approved drugs in the United States, so the practitioner must be familiar with the laws and regulations related to extralabel use. Drugs can be used extralabel in food animals only under specific circumstances and can be used only for therapeutic purposes. Drugs that are illegal in small ruminants include chloramphenicol; clenbuterol; diethylstilbestrol; dimetridazole, ipranidazole, and other nitroimidazoles such as metronidazole; dipyrone; fluoroquinolones; glycopeptides; nitrofurans; furazolidone; and extralabel use of medication in feed. It is also illegal to use any drug that results in residues above established tolerances or safe levels.

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Appendix

Contact Information and Resources for Laws and Regulations Pertaining to Drug Use in Small Ruminants

Contacts

Food and Drug Administration Center for Veterinary Medicine
Communications Staff
7500 Standish Place, HFV-12
Rockville, MD 20855
Telephone: (301) 594-1755

Food and Drug Administration Center for Veterinary Medicine
Office of Surveillance and Compliance
Director, Dr. Linda Tollefson
Telephone: (301) 827-6644

American Veterinary Medical Association
1931 North Meacham Road, Suite 100
Schaumburg, IL 60173
Telephone: (847) 925-8070
Fax: (847) 925-1329

Food Animal Residue Avoidance Databank
Telephone: 1-888-US-FARAD

Minor Use Program (NRSP-7)
National Coordinator, Dr. John Babish
508 White Church Road
Brooktondale, NY 14817
Voicemail: (607) 539-6126
Fax: (607) 539-9905
E-mail: jgb7@cornell.edu

Web Sites

Food and Drug Administration Center for Veterinary Medicine
http://www.fda.gov/cvm

FDA-approved Animal Drug Products Online Database System
http://dil.vetmed.vt.edu/

Guidance for Industry on FDA Approval of Drugs for Minor Species and Minor Uses
http://www.fda.gov/cvm/fda/infores/guidelines/minorgde.pdf

Minor Use Animal Drug Program
http://www.nrsp-7.org/

American Veterinary Medical Association AMDUCA Flowchart
(This document is in the member center and may be accessed only by American Veterinary Medical Association members.)
http://www.avma.org/scienact/amduca/amduca2.asp

Food Animal Residue Avoidance Databank
http://www.farad.org

National Library of Medicine Medline Database (for searching for pharmacokinetic data)
http://igm.nlm.nih.gov/

UPDATE ON SMALL RUMINANT MEDICINE 0749-0720/01 $15.00 + .00

ADVANCED REPRODUCTIVE TECHNIQUES IN GOATS

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and Juan E. Romano, DVM, MS

Several topics pertaining to reproduction in goats have been covered in previous issues of the *Veterinary Clinics of North America: Food Animal Practice*.[16, 23, 27, 29, 42] Those that are applicable to reproductive technology include out-of-season breeding, the use of ultrasonography in reproductive management, artificial insemination, and embryo transfer. Topics for which much of our current information has been acquired in the past decade, including early pregnancy diagnosis, follicular dynamics, follicular aspiration, in-vitro maturation/fertilization/culture, and cloning are also presented.

DIAGNOSIS OF PREGNANCY

Ultrasonography

The use of ultrasonography for reproductive tract evaluation in small ruminants is well established, and many evaluations of its use are available.[6, 7, 29, 38, 52, 53] Variables that affect the efficiency and accuracy of the procedure include the type of transducer, facilities and equipment used for restraint of the animals, size and body condition of the animals, stage of gestation, and the experience of the operator. Goats can be scanned transabdominally in the right inguinal region or transrectally, depending on the equipment available and the perceived reproductive

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