FARAD Digest

Drugs approved for small ruminants

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For the purpose of this FARAD Digest, small ruminants are considered to include sheep, goats, deer, and camelids. In the United States, the small ruminant population is low, and they are all considered minor species under the Food, Drug, and Cosmetics Act (**Table 1**). Minor species are defined by exclusion from major species (ie, cats, dogs, horses, swine, cattle, chickens, and turkeys). In the United States, sheep were only considered to be minor species in regard to efficacy and target animal safety requirements and remained a major species when human food safety was being evaluated. This exception was attributed to the high consumption of lamb and mutton at the time of the original classification in 1983. It was not until August 2002[4] that the sheep drug approval process was amended so that sheep were reclassified as a minor species with regard to human food safety requirements. Classification as a minor species allows the FDA flexibility in permitting new drug applications when

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Table 1—Drugs approved for various small ruminants and the US populations for those species

Active ingredient	Sheep 7.82 × 10⁶*	Goats[1] Fiber 2 × 10⁶,* milk & meat 2 × 10⁶	Deer[2] Wild 26 × 10⁶,* farmed 100 × 10³	Camelids[3] 175 × 10³*†	Drug availability
Albendazole	A	NA			OTC
Amoxicillin	NA				
Carfentanil citrate					Rx & C-II
Ceftiofur sodium	A, ANRSP-7	A, ANRSP-7	A		Rx
Chlortetracycline	A				OTC
Clorsulon		NA			
Decoquinate	A, ANRSP-7	A, ANRSP-7			OTC
Fenbendazole	A, ANRSP-7	A, ANRSP-7			Rx & OTC
Follicle stimulating hormone	A				Rx
Ivermectin	A	NA	A, ANRSP-7		OTC
Lasalocid	A				OTC
Levamisole	A	NA			OTC
Monensin		A, ANRSP-7			OTC
Morantel tartrate		A, ANRSP-7			OTC
Naltrexone			A		OTC
Neomycin	A	A			OTC
Neostigmine	A				Rx
Oxytetracycline	A				OTC
Oxytocin	A				Rx
Penicillin G (procaine)	A				OTC
Selenium & vitamin E	A				Rx
Tilmicosin	A, ANRSP-7				Rx
Xylazine hydrochloride	A				Rx
Zeranol	A				OTC

*United States population of the species. †Camelid population represents 145,000 llamas and 30,000 alpacas. A = Drug approved for this species. ANRSP-7 = Approvals that were obtained using a National Research Support Program #7 (NRSP-7) public master file. NA = No approval; National Research Support Program #7 has developed a public master file, but no manufacturer has used it to obtain an approval. OTC = Over-the-counter drug. Rx = Prescription drug. C-II = Schedule II drug.

extrapolating already accepted efficacy and safety data from a major species (eg, in the case of the small ruminants, it is cattle) to support new minor species claims. The reduction in regulatory requirements is supposed to act as a stimulus to gain new drug approvals in minor species; however, this has not worked well, as many approved drugs for cattle have not been approved for many of these small ruminants (**Table** 1 and **2**). In fact, most new animal drug approvals for minor species have been obtained through partnerships between the USDA-sponsored Agriculture Experimental Station-based program National Research Support Program #7 and pharmaceutical companies.

Clinical needs—This review of drugs approved for use in small ruminant species quickly demonstrates the problems facing minor species in gaining support of pharmaceutical companies pursuing drug approval (Table 1). Camelids (llamas and alpacas) have no drugs approved for use, and only 4 drugs are approved for cervidae (deer). Goats are marginally better off with 6 marketed drugs, compared with sheep, which have 16. What makes these observations of even more concern to small ruminant producers and veterinarians is the limit in scope of approved therapeutic indications (**Table** 2 and **3**). The 2001 National Animal Health Monitoring System Survey[5] found that 80% of diseases in sheep were related to gastrointestinal parasites, respiratory tract infection, mastitis, and footrot, and they respectively ranked as the second, third, and fifth (the last 2 combined) causes of death in flocks surveyed. A 1996 survey of small ruminant veterinarians and producers[6] reflected similar needs, although they ranked

Table 2—Food and Drug Administration information for drugs approved for use in sheep and goats as of June 2003

				Sheep			Goats		
Active ingredient	**Drug availability**	**Indication**	**Route**	**Dose***	**WDT meat (d)**	**WDT milk (h)**	**Dose**	**WDT meat (d)**	**WDT milk (h)**
Albendazole	OTC	Anthelmintic	PO	7.5 mg/kg	7	n/v			
Ceftiofur sodium	Rx	Antimicrobial, respiratory tract disease	IM & SC	1–2 mg/kg	0	0	1–2 mg/kg	0	0
Chlortetracycline calcium	OTC	Antimicrobial, prevent vibriosis, growth promotant	PO	80 mg/animal [vibriosis] 20–50 g/ton feed	0	n/v			
Decoquinate	OTC	Coccidiostat	PO	0.5 mg/kg	n/v	n/v	0.5 mg/kg	0	n/v
Fenbendazole	OTC or Rx	Anthelmintic	PO	5 mg/kg			5 mg/kg	6	0
Follicle stimulating hormone	Rx	Control of reproduction	IV, IM & SC	5–25 mg	0	n/v			
Ivermectin	OTC	Anthelmintic	PO	200 µg/kg	11	n/v			
Lasalocid (sodium)	OTC	Coccidiostat	PO	15–70 mg/animal	0	n/v			
Levamisole hydrochloride	OTC	Anthelmintic	PO	8 mg/kg	3	n/v			
Monensin (sodium)	OTC	Coccidiostat	PO	20 g/ton feed	0	n/v			
Morantel tartrate	OTC	Anthelmintic	PO				9.6 mg/kg	30	n/v
Neomycin sulfate	OTC	Antimicrobial, colibacillosis	PO	22 mg/kg/d	2	n/v	22 mg/kg/d	3	n/v
Neostigmine methylsulfate	Rx	Rumen & intestinal stimulant	IM & SC	0.02 mg/kg	0	n/v			
Oxytetracycline dihydrate pre-mix	OTC	Antimicrobial, growth promotant, colibacillosis	PO	10–20 g/ton [growth] 22 mg/kg [therapeutic]	0 5	n/v			
Oxytetracycline hydrochloride & polymyxin B sulfate	OTC	Antimicrobial, ocular infections	Ophthalmic	2–4X/d	0	n/v			
Oxytocin	Rx	Uterine contraction stimulant	IV, IM & SC	30–50 U/ewe	0	n/v			
Penicillin G (procaine)	OTC	Antimicrobial, respiratory tract disease	IM	6,000 U/kg	8–9	n/v			
Selenium (sodium selenite) & vitamin E	Rx	Treat & prevent white muscle disease	IM & SC	1 mL/18 kg	14	n/v			
Tilmicosin phosphate	Rx	Antimicrobial, respiratory tract disease	SC	10 mg/kg	28	n/v			
Zeranol	OTC	Growth promotant	SC	12 mg pellet [lambs]	40	n/v			

*Doses cited in Table 4 and 5 are in mg/kg but can be converted to mg/lb by dividing the dose by 2.2. Nonmetric versions of the tables are available by contacting the authors.

WDT = Withdrawal time. n/v = Convention to indicate the FARAD database has no value for that field; it may be that it is not available, or it may be inappropriate (eg, a milk withdrawal time for a nonlactating species).

See Table 1 for remainder of key.

pneumonia higher than mastitis and footrot. The authors argued that the extent of **extralabel drug use (ELDU)** in the small ruminant industry necessitates the need for increased research relating to preharvest safety of drugs and residue depletion. Two new antimicrobials have been approved in recent years—ceftiofur for sheep and goats and tilmicosin for sheep only. Both antimicrobials are limited to use by licensed veterinarians. Notably, there are neither drugs for treatment of mastitis nor any anti-inflammatory or analgesic drugs approved for small ruminants.

It is obvious that with so few approved small ruminant drugs, the reliance on ELDU is extremely high. AMDUCA enabled veterinarians acting within the constraints of a valid veterinarian-client-patient relationship to use drugs approved in other species for the relief of pain and suffering. This required the veterinarian to establish a substantially extended withdrawal period supported by appropriate scientific information. For the most part, this has been supplied by FARAD Access Centers in one-on-one, expert-mediated consultations. There have been a number of FARAD Digest articles[6-8] that gave **withdrawal intervals (WDIs)** after ELDU. These WDIs are not officially approved FDA **withdrawal times (WDTs)**, but they have been derived by FARAD using FDA pharmacostatistical methods, often with a limited data set (**Table 4**). The prohibition of ELDU in feed has become a problematic issue with AMDUCA. The FDA-CVM has recognized this problem and has issued guidance for the adoption of lower levels of regulatory concern for ELDU in feed intended for use in minor species.[10] This regulatory discretion is still limited (minor species only, within a valid veterinarian-client-patient relationship, a prescription lifespan limited to 6 months, and a formulation identical to that approved for a major species).

FARAD continues to receive requests for small ruminant ELDU drug WDTs. A previous FARAD Digest[11] described the methods the program used to derive the recommended WDIs. Problems occur when practitioners assume that cattle WDTs can be applied to

Table 3—Food and Drug Administration information for drugs assigned for use in deer as of June 2003

Active ingredient	Drug availability	Indication	Route	Dose	WDT meat (d)	WDT milk (h)
Carfentanil citrate	Rx & C-II	μ agonist, opioid chemical immobilization	IM	5–20 μg/kg [Cervidae, elk & moose]	30	n/v
Naltrexone hydrochloride	Rx	Opioid antagonist, reversal of carfentanil	IV & SC	100 mg/mg carfentanil [Elk & moose]	45	n/v
Ivermectin	OTC	Systemic parasiticide	SC	0.2 mg/kg [Reindeer]	56	n/v
Xylazine hydrochloride	Rx	α-2 agonist sedative and analgesic	IV, IM & SC	0.5–2 mg/kg [Deer, elk, fallow deer, mule deer, sika deer, white-tailed deer]	n/v	n/v

Data are from FARAD's US Approved Animal Database and were originally extracted from FDA Federal Register notice.
See Tables 1 and 2 for key.

Table 4—Withdrawal intervals (WDIs) for some common instances of extralabel drug uses previously published in *JAVMA* FARAD Digests

				Sheep		Goats	
Drug	Reference	Dose	Route	WDI meat (d)	WDI milk (h)	WDI meat (d)	WDI milk (h)
Acepromazine	7	< 0.13 mg/kg	IV	7	48	7	48
	7	< 0.44 mg/kg	IM	7	48	7	48
Ketamine	7	< 2 mg/kg	IV	3	48	3	48
Lidocaine with epinephrine	7		Epidural	1	24	1	24
Thiopental	7	< 5 mg/g	IV	1	24	1	24
Xylazine	7	0.016–0.1 mg/kg	IV	5	72	5	72
	7	0.05–0.3 mg/kg	IM	10	120	10	120
Yohimbine	7	< 0.3 mg/kg	IM	7	72	7	72
Aspirin	8	All usual doses		1	24	1	24
Ketoprofen	8	3.3 mg/kg, IV, q 24 h × 3	IV or IM	7	24	7	24
Ivermectin	9	0.2 mg/kg	PO			11	6
	9	0.2–0.4 mg/kg	PO			14	9
	9	0.2 mg/kg	SC			35	40
	9	0.5 mg/kg	Topical			n/v	7
Moxidectin	9	0.2 mg/kg	PO			14	n/v
	9	0.5 mg/kg	PO			23	n/v

See Tables 1 and 2 for key.

Table 5—Comparison of FDA label doses and WDTs for drugs that are approved in cattle and small ruminants

	Cattle			Sheep		Goats		
		WDT			WDT		WDT	
Drug	Dose	Meat (d)	Milk (h)	Dose	Meat (d)	Dose	Meat (d)	Milk (h)
Albendazole	10 mg/kg	27	n/v	7.5 mg/kg	7			
Ceftiofur sodium	0.5–1 mg/kg	0	0	1–2 mg/kg	0	1–2 mg/kg	0	0
Chlortetracycline	0.1 mg/kg	0	n/v	80 mg/head	0			
Decoquinate	0.23 mg/kg	0	n/v	0.5 mg/kg	0	0.5 mg/kg	0	n/v
Fenbendazole	5 mg/kg	8	n/v			5 mg/kg	6	0
Follicle stimulating hormone	10–50 mg/animal	0	n/v	5–10 mg/head	0			
Ivermectin	200 µg/kg	24	n/v	200 µg/kg	11			
Lasalocid	0.25–1 mg/kg	0	n/v	15–70 mg/head	0			
Levamisole	1.7 µg/kg	2	n/v	8 mg/kg	3			
Monensin	0.1–1 mg/kg	0	n/v			20 g/ton feed	0	n/v
Morantel tartrate	5.7 mg/kg	14	n/v	9.6 mg/kg	30			
Neomycin	22 mg/kg	1	n/v	22 mg/kg	2	22 mg/kg	3	n/v
Neostigmine	0.02 mg/kg	n/v	n/v	0.02 mg/kg	0			
Oxytetracycline	0.2 mg/kg, 3–5 mg/kg	0, 28	n/v	22 mg/kg	5			
Oxytocin	100 U/cow	0	n/v	30–50 U/ewe	0			
Penicillin G (procaine)	6,000 U/kg	4	n/v	6,000 U/kg	9			
Selenium & vitamin E	1 mL/kg	30	n/v	1 mL/18 kg	14			
Tilmicosin	10 mg/kg	28	n/v	10 mg/kg	28			
Zeranol	3 × 12-mg pellets/animal	0	n/v	1 pellet	40			

See Tables 1 and 2 for key.

small ruminant species (**Table 5**). Those drugs with zero WDTs are similar between species with the notable exception of oxytetracycline. Oxytetracycline's labeled use in cattle has a zero WDT, whereas the label for sheep has a 5-day WDT, presumed to be based on the sheep dose being 100-fold greater than that used in cattle. Another danger in species extrapolation is toxicity. Tilmicosin is approved for treatment of respiratory tract disease in cattle and sheep but is toxic to goats.[12] Another more recent concern is the practice of oral administration of Cydectin (moxidectin) to goats that are not responding to fenbenzdazole or ivermectin. Although moxidectin is approved for topical use in cattle with zero milk and meat WDTs, this does not imply that the meat and milk WDTs will be zero if given orally to goats. In fact, FARAD has determined that the meat WDI in goats can be as much as 23 days after administration of the approved cattle dose of 0.5 mg/kg (0.22 mg/lb; Table 3).

Future outlook—With the sheep industry slowly declining and the goat population gaining, the drug availability situation is troublesome. Today, the need for new drug approval exceeds the pharmaceutical industry's research and development capacity and financial ability. However, there is the MUMS bill before Congress to promote drug availability for minor uses in major species and general use in minor species. The bill establishes new ways to lawfully market new animal drugs and provides a process for designating certain drugs to qualify for financial incentives. It will also include the establishment of division within the FDA-CVM to overlook and facilitate new minor species drug approvals.

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