SECTION VI-1
VETERINARY DRUGS APPROVED FOR USE IN LACTATING DAIRY SHEEP

1. VETERINARY DRUGS APPROVED FOR USE IN LACTATING DAIRY SHEEP

There are no veterinary medicines in Canada that are approved for use in lactating dairy sheep, where the milk is intended for food. This means that all drug use is "extra label" and that there are no published withdrawal times for milk. This presents a dilemma to sheep producers and their veterinarians who wish to effectively treat and control infections in their ewes and yet be assured that appropriate withdrawals for milk and meat are followed so that no residues enter the food chain (see Section V.5). Along with working closely with your flock veterinarian with whom you have a valid veterinary-client-patient relationship (VCPR) (Section VI.1.2), this section will help to give you advice on how to best accomplish this goal.

1.1 WHAT IS EXTRA LABEL DRUG USE (ELDU)?

1.1.1 DEFINITION

As defined by Health Canada[1], Extra-Label Drug Use (ELDU), or "off-label use" is:

> *"The use or intended use of a drug approved by Health Canada in an animal in a manner not in accordance with the label or package insert. It also includes the use of all unapproved drugs, including unapproved bulk active pharmaceutical ingredients (APIs) and compounded drugs."*

Although defined by Health Canada, this is a term that is used worldwide.

While we traditionally think of ELDU in terms of using a drug not approved for use in sheep as a species (e.g. approved for cattle but not sheep), it also includes using it differently than the directions on the label, i.e.:

- Different dose (*e.g. using a drug at 3 mL/45 kg when it is labelled at 2.5 mL/45 kg*)
- Different frequency (*e.g. giving a drug twice per day when it is labelled at once per day*)
- Different route of administration (*e.g. giving the drug under the skin when it is supposed to go in the muscle*)
- Different duration (*e.g. if the label says only to give for 3 days and it is administered for 5 days*)
- Different indication (*e.g. when it is labelled to treat pneumonia and it is used to treat mastitis*).
- Different class of animal (*e.g. when it is labelled for use in a lamb and it is used in a lactating dairy ewe*)

1.1.2 REGULATORY ISSUES

Prescription veterinary medicines can only be purchased from a veterinarian and with a valid veterinary-client-patient relationship (see Section VI.1.2). Written instructions for ELDU need to be

[1] http://www.hc-sc.gc.ca/dhp-mps/vet/label-etiquet/index-eng.php

provided by your veterinarian when the drug is dispensed when different from the label. The veterinarian and producer are responsible for making sure the drug is used correctly and drug residues do not enter the food chain.

If the drug is purchased at a Livestock Medicines Outlet (i.e. over-the-counter medications), and it to be used extra-label, it is strongly advised to only use with a veterinary prescription (required by those on the Canadian Sheep and Lamb Food Safe Farm Practices program). N.B. In Quebec, all livestock medicines are purchased from a licensed veterinarian. Inappropriate ELDU may result in:

- Residues in the milk which is dangerous for people and will harm cheese production
- Residues in the meat, which is dangerous for people
- Inappropriate treatment of animals resulting in treatment failure and/or adverse reactions in the sheep
- Risk of development of antimicrobial resistance (AMR) because of failure to treat the infection correctly or over-treatment resulting in AMR in other bacteria in the animals.

1.1.3 HOW ARE WITHDRAWAL TIMES DETERMINED WITH ELDU?

MAXIMUM RESIDUE LIMIT (MRL)

As defined by Health Canada[2], Maximum Residue Limit (MRL) is:

> "*The amount of residue that could remain in the tissue or food product derived from a food producing animal that has been treated with a veterinary drug*."

The MRL for a drug or chemical is usually measured in very tiny amounts, e.g. ppm (parts per million), and is determined through scientific experiments as being the highest level of a drug or chemical that is safe for a person to consume daily over their life-time with no risk to their health.

Withdrawal times are calculated as the amount of time that it takes for that drug to leave the body of a treated animal to at least as low as the MRL. Sheep often metabolize and excrete drugs differently than cattle or goats, so we can't assume that because the withdrawal for cattle is a certain time-length, it will be the same for sheep.

MINIMUM DETECTION LIMIT (MDL)

This is a property of the test being used to detect presence of a drug in the milk. The test can detect presence of a drug down to a certain limit. Usually this level is lower (i.e. less) than the MRL established for drugs approved for use in lactating dairy animals (in Canada – this is limited to dairy cows).

USING WITHDRAWALS LISTED FOR OTHER SPECIES OR SHEEP IN OTHER COUNTRIES

As no drugs are approved for lactating dairy sheep, the processor will use the MDL as the MRL. This value is likely lower than the published MRL for dairy cows. Because of this, withdrawals approved for dairy cows may result in **a positive test** for dairy sheep. When selecting a milk test to use at home, make sure its MDL is as low as that which is used by the processor.

[2] http://www.hc-sc.gc.ca/dhp-mps/vet/mrl-lmr/index-eng.php

THINGS THAT MAY PROLONG A WITHDRAWAL PERIOD FOR MILK

- The sheep is milked once/day versus twice/day
- Milk volume per day is low, e.g. at the beginning and end of lactation resulting in concentration of a drug in the milk
- The drug is administered incorrectly (e.g. subcutaneous versus intramuscular) resulting in the drug being poorly absorbed and eliminated
- Too large a volume is administered in one spot, again resulting in the drug being poorly absorbed and eliminated
- Injections are given in the same place on the animal, again resulting in the drug being poorly absorbed and eliminated
- The ewe is ill which might harm its ability to properly metabolize and eliminate the drug
- And of course, giving too high a dose, increasing the frequency of treatment, prolonged administration, etc.

CANADIAN GFARAD

Fig. 1.

The Canadian gFARAD[3] (global Food Animal Residue Avoidance Database) is an initiative based at both the University of Saskatchewan (Saskatoon, Saskatchewan) and the University of Guelph (Guelph, Ontario). CgFARAD provides information on food animal residues from drugs and other chemicals used in the food production industry. In order to help determine an appropriate withdrawal for meat or milk from a food animal species, veterinarians can submit a request to CgFARAD, and then relay this valuable information onto their respective clients, to ensure that all appropriate withdrawal times are being taken before milk or meat is put into the food chain.

Issues with CgFARAD include: turnaround time may be days to several weeks depending on availability of information; limitations of available information, i.e. sometimes they are unable to determine a withdrawal based on information published; and the potential cost. Currently the service is not charged but a lack of government funding for this program is a threat.

1.1.4 IS THIS DRUG SAFE TO USE?

Despite the fact that there are no drugs approved for use in lactating dairy sheep in Canada, we must be sure that any drug which is used can be administered safely to the animal, it is effective for the disease being treated, and that we can properly estimate a safe and reasonable withdrawal for milk and meat.

DRUG IDENTIFICATION NUMBER (DIN)

A drug identification number (DIN) is a specific number that is allocated to each drug that is approved for use through the Veterinary Drug Directorate, Health Canada[4]. This code is located on the label of each approved drug, with the three letters "DIN", followed by an eight-digit number. DIN codes can be used in many cases, such as recall of drug products, and quality monitoring of drug products.

[3] http://www.cgfarad.usask.ca/
[4] http://www.hc-sc.gc.ca/dhp-mps/prodpharma/activit/fs-fi/dinfs_fd-eng.php

If you have purchased a drug and it does not have a DIN on the label, then it does not meet the legal requirements of being used as a drug in Canada. This applies to both human and veterinary drugs.

THE LABEL OF A VETERINARY DRUG IN CANADA

A drug sold in Canada must have a label attached to it and is accompanied by a package insert or box containing additional required information. When you purchase a drug, save all the inserts and boxes and do not "repackage" drugs into other containers.

The following information should be kept where it can be readily consulted. A good practice is to keep a binder of labels, inserts etc. where you store your livestock medicines. This information can also be readily found through accessing the Canadian Compendium of Veterinary Products website[5].

In addition to the requirement of a DIN – which must appear on the drug label, clear and up-front, the label must contain:

1) The words "**For Veterinary Use Only**", i.e. not to be used in humans
2) "*Pr*" means that it is by veterinary prescription only i.e. must be prescribed by a veterinarian licensed to practice in the province in which the animal resides. If no "*Pr*" is present on the label, then no prescription is required
3) Brand name of the product – registered with the Veterinary Drug Directorate, Health Canada. It is accompanied by the name of the manufacturer and its Canadian address.
4) A list of medicinal (active) ingredients and their concentration in the product (e.g. mg of drug "X" per mL of product). Often preservatives, diluents and other non-medicinal ingredients are included – although some are proprietary and may not be explained in full.
5) Formulation indicates if it is an injectable product, intramammary, oral or topical.
6) Instructions for administration
   a) Dosage - usually in mL or mg of product per measure of the animal's body weight; e.g. 3 mL per 45 kg bw or 2 mg/kg bw.
   b) Route of administration (e.g. oral, in feed or water, topical, intramammary, intravenous, intramuscular or subcutaneous)
   c) Frequency and duration of treatment (e.g. once/day for 3 days)
   d) Animal and class of animal (e.g. lambs)
   e) Indication (e.g. for the treatment of pneumonia)
7) Warnings and cautions about
   a) Health hazards for humans and animals either through direct contact (e.g. may burn if get the drug in your eyes), adverse reactions in animals (e.g. may be harmful to the fetus of pregnant animals, e.g. do not administer to horses), or through residues in food products.
   b) Withdrawals for meat
   c) Withdrawals for milk if allowed for use in lactating dairy animals
   d) Restrictions, e.g. do not use in lactating dairy animals
8) Production lot number (important for recalls or if an adverse reaction occurs)
9) Expiry date (important because the drug won't work if too old)
10) Storage information (e.g. must be refrigerated at < 4°C; do not freeze; do not expose to sunlight)

[5] http://cdmv.naccvp.com/?u=country&p=msds

USING DRUGS NOT APPROVED FOR USE IN CANADA

At this point, it is legal for producers to purchase drugs from outside Canada for "own use", i.e. to use in the treatment of their own animals[6]. **This is not in compliance with the Canadian Sheep and Lamb Food Safe Farm Practices program.** Possible issues arising from using these drugs include:

- The product does not contain the level of drug indicated on the label;
- The product contains adulterants which may be harmful to the animal or to people;
- The product is expired and has been repackaged;
- The product has not been shown by properly conducted science to be effective or safe in animals and humans;
- The quality of the manufacturing process of the product is poor or unregulated.

1.2 WHAT IS A VETERINARY – CLIENT – PATIENT RELATIONSHIP (VCPR)?

The Veterinary-Client-Patient Relationship[7] (VCPR) is a key component of ELDU, and is outlined by Health Canada as:

- *"The client (owner or owner's agent of the animal [s]) has given the responsibility of medical care to the veterinarian and has agreed to follow the instructions of the veterinarian, and;*
- *The veterinarian has assumed the responsibility from the client for making clinical judgment regarding the health of the animal(s), the need for medical treatment, and for ensuring the provision of ongoing medical care for the animal(s), and;*
- *The veterinarian has sufficient knowledge of the health status of the animal(s) and the care received or to be received. The knowledge has been obtained through a recent examination of the animal(s) and the premises where they are (it is) kept or through a history of medically appropriate and timely examinations and interventions, and;*
- *The veterinarian is readily available, or has made the necessary arrangements with another veterinarian, for ongoing medical care in case of adverse reactions or therapy failure."*

Without having a reliable VCPR, the prescription of ELDU could pose potential health issues for both treated animals, and subsequent human health from consumption of these food products.

[6] http://www.hc-sc.gc.ca/dhp-mps/vet/faq/faq_unapproved-nonapprouves_drugs-medicaments-eng.php
[7] http://www.hc-sc.gc.ca/dhp-mps/vet/label-etiquet/pol_eldu-umdde-eng.php#fnb3-ref