

EXTRA-LABEL DRUG USE (ELDU) AND THE ANIMAL MEDICINAL DRUG USE CLARIFICATION ACT (AMDUCA) – HOW THEY IMPACT THE PRODUCER, VETERINARIAN, PROCESSOR AND CONSUMER

John R. Middleton
University of Missouri
Columbia, Missouri, USA

Introduction

Therapy of animal disease has evolved significantly over the last 100 years. The introduction of antibiotics and other therapeutic agents has allowed us to treat infection and better alleviate pain and suffering. A wide variety of pharmaceutical agents are marketed for treatment of humans and animals. However, only a minority of these products are specifically labeled for use in animals with an even smaller subset being labeled for use in dairy cattle. Hence, occasions arise where a drug must be used in an extra-label fashion, that is, in a manner other than specified on the product label or package insert. Extra-label drug use (ELDU) is routinely employed by veterinarians to alleviate pain and suffering in ill animals. The Animal Medicinal Drug Use Clarification Act (AMDUCA) was enacted in 1994 and provides guidelines for ELDU in animals.

ELDU

In general, three classifications of drugs are found on dairy farms 1) over the counter (OTC) drugs, 2) prescription drugs, and 3) OTC or prescription drugs which are not used in according to label directions. Over the counter products can be purchased without a veterinary prescription. Prescription drugs are those which must be dispensed by or on the order of a veterinarian and will carry one of the following statements on the label: “CAUTION: Federal Law restricts this drug to use on or by the order of a licensed veterinarian” or “CAUTION: Federal Law restricts this drug to use on or by the order of a physician”.

Extra-label drug use occurs when a product is used in a manner other than specified on the label such as when a drug is used at a different dosage, dosing frequency, route of administration, in a different class of animal, or the disease being treated is not specified on the label. When OTC drugs are NOT used according to the manufacturer’s label directions they require a prescription.

Example:

Drug: Procaine Penicillin G (available OTC)

Label direction: Administer 3,000 units/lb (6,600 units/kg) intramuscularly (IM)

Commonly used dose in dairy cattle: 10,000-15,000 units/lb (22,000-33,000 units/kg)

Commonly used routes of administration: subcutaneously or intramuscularly

Comment: As commonly used this drug requires a prescription from a veterinarian even though it is available OTC. At the prescribed higher dosage, the label milk and meat withholding times no longer apply!

AMDUCA

The Animal Medicinal Drug Usage Clarification Act amended the Federal Food Drug and Cosmetic Act to allow **licensed veterinarians to prescribe extra-label uses of Food and Drug Administration (FDA)-approved animal and human drugs in animals.** Extra-label drug usage can be prescribed for **THERAPEUTIC PURPOSES ONLY** (when the health of an animal is threatened or suffering or death may result from failure to treat) and prescription must follow the specific guidelines summarized below. Extra-label drug use **CANNOT** be practiced for enhancing production.

Requirements for ELDU (From 21 CFR 530.3 and 530.20 and AVMA Informational Outline of AMDUCA, 2007)

The following conditions must be met for a permitted extra-label drug use in food-producing animals.

- There is **NO** approved animal drug that is labeled for such use that contains the active ingredient which is in the required dosage form and concentration, except where a veterinarian finds, within the context of a valid veterinarian-client-patient relationship, that the approved animal drug is clinically ineffective for its intended use.
- A valid-veterinarian-client-patient relationship exists when:
 - A veterinarian has assumed responsibility for making medical judgments regarding the health of (an) animal(s) and the need for medical treatment, and the client (owner of animal(s) or caretaker) has agreed to follow the instructions of the veterinarian;
 - 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
 - The practicing veterinarian is readily available for follow-up in case of adverse reactions or treatment failure. Such a relationship can only exist 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.
- Prior to prescribing or dispensing an FDA-approved animal or human drug for extra-label use in a food-producing animal the veterinarian must:
 - Make a careful diagnosis and evaluation of the conditions for which the drug is to be used;
 - Establish a substantially extended withdrawal period for milk, meat, or other products supported by scientific information, if applicable;
 - Institute procedures to assure that the identity of the treated animal or animals is carefully maintained; and
 - Take appropriate measures to assure that assigned timeframes for withdrawal are met and **NO ILLEGAL DRUG RESIDUES** or residues which may present a risk to human health occur in any food-producing animal or food product subjected to extra-label treatment.

- Use of an FDA-approved human drug or of an animal drug approved only for use in animals not intended for human consumption must meet the following additional criteria:
 - Such use must be accomplished in accordance with an appropriate medical rationale;
 - If scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food-products will not enter the human food supply.
 - Extra-label use of an approved human drug in a food-producing animal is not permitted if an animal drug approved for use in food-producing animal can be used in an extra-label manner for the particular use.
- ELDU is permitted only by or under the supervision of a veterinarian, and a valid Veterinarian/Client/Patient relationship is a prerequisite for ALL ELDU.
- ELDU is allowed only for FDA-approved animal and human drugs.
- Rules apply to dosage form drugs and drugs administered in water. ELDU in feed is prohibited.
- FDA prohibition of a specific ELDU precludes such use.

Recordkeeping Requirements (From AVMA Informational Outline of AMDUCA, 2007)

- Identify the treated animals either as a group or individuals.
- Record animal species, number of animals, and condition(s) being treated.
- Record the established name and active ingredient of the drug used.
- Record the dosage, dosing frequency, and duration of treatment.
- Record the specified withholding times for milk and dairy beef.
- Records must be kept for 2 years after treatment and the FDA must have access to these records to estimate risk to public health.

Labeling Requirements (From 21 CFR 530.12)

- Name and address of the prescribing veterinarian and if dispensed by a pharmacy the name and address of the dispensing pharmacy.
- Established name of the drug or drugs (if formulated from more than one drug).
- Directions for use including the class/species or identification of the animal herd, flock, pen, lot or other groups of animals being treated; the dosage frequency and route of administration; and duration of therapy.
- Any cautionary statements
- 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.

Compounding Drugs (From 21 CFR 530.13)

Compounded drugs are those which are made from multiple ingredients by a veterinarian or pharmacist. Compounding does not include mixing, reconstituting, or other such acts that are

performed in accordance with directions contained in an approved labeling provided by the product's manufacturer, e.g., mixing sterile water with Naxcel[®] to reconstitute for use.

Compounding from bulk drugs is prohibited. Extra-label drug use of product compounded from FDA-approved animal or human drugs is permitted if:

- There is NO approved animal or human drug that, when used as labeled or in conformity with AMDUCA in the available dosage form and concentration, will appropriately treat the diagnosed condition. Compounding from a human drug for use in food-producing animals will not be permitted if an approved animal drug can be used for the compounding;
- The compounding is performed by a licensed veterinarian or pharmacist within the scope of a professional practice;
- Adequate procedures and processes are followed to ENSURE THE SAFETY AND EFFECTIVENESS of the compounded product;
- The scale of the compounding operation is commensurate with the established need for compounded products (e.g., similar to that of comparable practices); and
- All relevant State laws relating to compounding of drugs for use in animals are followed.

More information on compounding can be found in: Guidance for FDA Staff and Industry, Compliance Policy Guides Manual. Sec. 608.400. Compounding of Drugs for Use in Animals.

Drugs Prohibited for use in Food-Producing Animals (From 21 CFR 530.41)

Table 1. Drugs Prohibited From Use in Food-producing Animals

| Drug Name | Common Examples | Notes |
|--|---|---|
| Chloramphenicol | Chloramphenicol | |
| Clenbuterol | Clenbuterol | |
| Colloidal Silver | No FDA-approved product | |
| Diethylstilbesterol (DES) | | |
| Dimethyl Sulfoxide (DMSO) – non-medical grade | Industrial grade DMSO | Medical-grade DMSO may be prescribed by a veterinarian in an extra-label manner to treat life-threatening conditions in dairy cattle, but under no circumstances should the product be stored on the operation for indiscriminant use by dairy personnel. |
| Dimetridazole, Ipronidazole, and other Nitroimidazoles | Flagyl [®] (Metronidazole) | |
| Dipyrrone | Novine [®] , No pain [®] , Dipyrrone [®] | No longer marketed |
| Estradiol cypionate (ECP) | No FDA-approved product | Any use in food animals is ILLEGAL |

| Drug Name | Common Examples | Notes |
|---|--|--|
| Fluroquinolones | Baytril 100 [®] (Enrofloxacin), A180 [®] (Danofloxacin) | Approved for use ONLY according to label; NOT approved for animals intended for dairy production |
| Furazolidine, Nitrofurazone and other Nitrofurans | Furacin Ointment | |
| Glycopeptides | Vancomycin | |
| Phenylbutazone in dairy cattle over 20 months of age | Phenylbutazone | |
| Sulfonamide drugs in lactating dairy cattle except approved use of sulfadimethoxine (Albon [®]) | Trimethoprim Sulfadiazine (TMP-SDZ) | |
| Adamantanes | | Prohibited in poultry |
| Neurominidase inhibitors | | Prohibited in poultry |

Examples of ELDU Which Do Not Comply With AMDUCA or Are Prohibited

Drug: Baytril 100[®]

Label direction: Indicated for the treatment of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida* and *Haemophilus somnus*. **WARNING:** Animals intended for human consumption must not be slaughtered within 28 days from the last treatment. DO NOT USE IN CATTLE INTENDED FOR DAIRY PRODUCTION. A withdrawal period has not been established for this product in pre-ruminating calves. Do not use in calves to be processed for veal.

ELDU on dairy farms: Treatment of diarrhea or respiratory disease in replacement heifer calves.

Comment: ELDU of Baytril[®] is prohibited. Cattle for dairy production include calves reared as dairy replacements, heifers, lactating and non-lactating cows, and bulls maintained for breeding purposes.

Drug: Ceftiofur Sodium (Naxcel[®])

Label direction: Administer by subcutaneous or intramuscular injection at the dosage of 0.5 to 1.0 mg (1.1-2.2 mg/kg) ceftiofur equivalents/lb body weight (1 to 2 ml reconstituted sterile solution per 100 lb body weight). Treatment should be repeated at 24-hour intervals for a total of three consecutive days.

ELDU on dairy farms: Intramammary instillation for treatment of intramammary infection.

Comment: Intramammary use of Naxcel[®] violates AMDUCA because Spectramast[®] contains the same active ingredient and is labeled for intramammary use to treat intramammary infection. In addition Naxcel[®] does not have a label claim for intramammary infection.

Drug: Banamine® (Flunixin meglumine)

Label Direction: 1.1 to 2.2 mg/kg (0.5 to 1 mg/lb; 1 to 2 ml per 100 lbs) of body weight given by slow intravenous administration either once a day as a single dose or divided into two doses administered at 12-hour intervals for up to 3 days. The total daily dose should not exceed 2.2 mg/kg (1.0 mg/lb) of body weight. Avoid rapid intravenous administration of the drug.

ELDU on dairy farms: Intramuscular injection.

Comment: Injecting Banamine® intramuscularly violates AMDUCA because ELDU cannot be practiced for convenience. The current drug approval is restricted to intravenous administration in cattle. ELDU of this product may lead to violative drug residues as intramuscular injection requires a longer withdrawal period to deplete the drug-related residue.

Drug: Aloe Vera

ELDU on dairy farms: Promoted as a treatment for mastitis, a cure for high somatic cell counts, as an aid for increasing milk production, and treatment of calf diarrhea.

Comment: There are no FDA-approved drugs containing Aloe Vera for treatment of the above listed diseases. Use of unapproved products is a violation of Item 15r of the Pasteurized Milk Ordinance and also violates AMDUCA.

How Do ELDU and AMDUCA Impact the Producer, Veterinarian, Processor and Consumer?

Food-producing animals and food producers come under continual scrutiny from the public. Public perception ultimately drives the market for food products from animals. One perception is that antibiotic use in animals is giving rise to widespread antimicrobial resistance. The scientific evidence to support this assertion is limited (Erskine, 2006). Nonetheless it is our responsibility to maintain a safe and wholesome food supply. In so doing, use of drugs on dairy farms needs to follow established guidelines. Adherence to these guidelines in conjunction with prudent use of drugs will hopefully ensure that our industry has continued access to therapeutic agents. Extra-label drug use must therefore be performed according to AMDUCA. A producer cannot administer drugs in an extra-label manner without prescription by a veterinarian. While it is the veterinarian's responsibility to oversee ELDU, it can be difficult to police usage on the farm. For example, if a producer has a herd of beef cattle as well as a herd of dairy cattle and his or her veterinarian has prescribed Baytril® for treatment of respiratory disease in the beef cattle, the producer CANNOT then decide to use it in a dairy replacement heifer with a cough as that would be ILLEGAL. Hence, it is as much the producer's responsibility as it is the veterinarian's to ensure that he or she follows the prescription for a particular drug. Lack of compliance with AMDUCA can potentially lead to violative milk and dairy beef residues or present other risks to human health which impact everyone. The impact on the producer can be lost milk and penalties which equate to negative income. The veterinarian may risk loss of licensure if he or she fails to comply with AMDUCA especially if he or she prescribes or administers a prohibited substance. The processor, much like the producer has to discard milk or dairy beef which impacts production costs and volume of finished product that can be delivered to the end user. Finally, if adulterated product escapes detection, the consumer can be potentially impacted by an adverse reaction to a compound or its metabolites in the finished product. Furthermore, inappropriate use of drugs, in particular antibiotics, may contribute to the development of antibiotic resistance because of inadequate dosage, dosing frequency, duration of treatment or improper route of administration.

Take Home Messages

- Whenever possible, use a product that is labeled for use in dairy cattle that contains the needed ingredient, in the proper dosage form, is clinically effective, and is labeled for the indication (disease) being treated.
- If ELDU must be practiced, it can only be performed on or by the order of a veterinarian in the context of a valid veterinary-client-patient relationship using an FDA-approved animal or human drug and prescription must follow all of the guidelines described above.
- Some drugs are prohibited from extra-label use in food animals (see above). The drugs on this list constantly change and it is the responsibility of the farm's veterinarian to stay abreast of changes to the list of prohibited substances and ensure that these products are not on the farm.
- More information, including a decision matrix on when ELDU is applicable can be found on the American Veterinary Medical Association's website:

www.avma.org/reference/amduca/amduca1.asp

References

An informational outline of the animal medicinal drug use clarification act (AMDUCA). 2007. American Veterinary Medical Association, Schaumburg, IL. www.avma.org/reference/amduca/amduca1.asp

Erskine, R. J. 2006. Overview of literature on antimicrobial resistance of mastitis pathogens. Proc. 45th Annual Meeting of the National Mastitis Council, pp 3-9.

Extralebel drug use in animals. 2006. Title 21, Volume 6, Code of Federal Regulations Part 530.1-530.41.

Item 15r – Drug and chemical control of grade “A” pasteurized milk ordinance. Document M-I-06-5. Pages 1-20.