

# Dairy Sessions

Moderators: Fred Gingrich, Trent Lartz, Lowell Midla, Dick Wiley

## Animal Medicinal Drug Use Clarification Act, extralabel drug use, and residue avoidance

Virginia R. Fajt, DVM, PhD, DACVCP

Texas A&M University College of Veterinary Medicine and Biomedical Sciences, 4466 TAMU, College Station, TX 77843-4466

### Abstract

Increased scrutiny of drug use by regulatory agencies and the general public requires dairy animal owners and dairy veterinarians to examine their drug decision-making processes and drug use policies. This presentation will review relevant legislation, regulations, and drug use guidelines to aid practitioners in making good decisions that maximize drug efficacy while maintaining a safe food supply. In addition, the ethical and professional issues underlying many drug selection and use issues will be considered.

**Key words:** dairy, AMDUCA, extra label, residues

### Résumé

Le contrôle accru de l'utilisation des médicaments par les agences de réglementation et le grand public fait en sorte que les propriétaires de bovins laitiers et les vétérinaires qui s'occupent de bovins laitiers doivent examiner leur processus de décision en égard aux médicaments et leur politique d'utilisation de ces médicaments. Cette présentation revoit les lois pertinentes, la réglementation et les lignes directrices concernant l'utilisation des médicaments afin d'aider les praticiens à faire des choix judicieux pour maximiser l'efficacité des médicaments tout en assurant un approvisionnement alimentaire sûr. En plus, les problèmes éthiques et professionnels associés à plusieurs aspects du choix et de l'utilisation des médicaments seront considérés.

### Introduction to the Legalities of Drug Selection and Use

One might think that outlining legal and illegal uses of drugs in cattle would be straight-forward. However, given the number (and mandates) of oversight agencies, the variety of production settings, and the myr-

riad production goals of dairy producers, it is not always clear-cut. Even legislation and regulations are subject to interpretation, since every contingency cannot be included in laws and rules, so guesses about interpretation are sometimes required. Governmental agencies that may be involved in overseeing drug selection and use in cattle include the Food and Drug Administration Center for Veterinary Medicine (FDA-CVM), the Environmental Protection Agency (EPA), the US Department of Agriculture Food Safety and Inspection Service (FSIS), the Drug Enforcement Agency (DEA), individual state veterinary medical boards (for links, see <http://www.aavsb.org/>), and individual state pharmacy boards (for links, see <http://www.nabp.net/>). FDA-CVM approves drug labels and pursues legal action against tissue residue violations; EPA approves pesticide labels; FSIS inspects cattle harvest ante- and postmortem and tests for drug residues; DEA defines and enforces regulations related to the distribution and use of controlled substances; veterinary medical boards define and enforce veterinary practice acts; and pharmacy boards define and enforce pharmacy and drug distribution law. For dairies, there is also the National Conference on Interstate Milk Shipments (NCIMS), a partnership among the Public Health Service of the US Department of Health and Human Services, FDA, and non-federal regulatory bodies, which together and separately provide input to and enforce the Pasteurized Milk Ordinance (PMO), which describes and defines procedures for milk sanitation and prevention of milkborne disease. A small part of the PMO relates to drug selection and use practices, notably location and labeling of drugs, required treatment records, and "Appendix N" (drug residue testing and farm surveillance).

Given the alphabet soup of regulators and the mix of state and federal law, it is no wonder that confusion exists. One approach is to step back and consider the purpose of all these regulators: safe and effective medications and a safe and wholesome food supply. Keeping those purposes in mind will aid veterinarians, farmers,

and ranchers in making legal and effective decisions about therapeutics. When realizing that every mouthful of product is not tested and deemed safe but risk-based and statistical approaches are used, self-regulation and self-assessment become even more important to prudent drug use practices.

### Label and Extralabel Drug Use

Is it important to know whether a particular use is extralabel or not? If the outcome is improved animal health and a safe and wholesome food supply, the answer could easily be “no.” The important considerations are: is the drug use safe for animals (in the balance, of course, since no drug is completely 100% safe)? Is the drug likely to be effective in the animal(s)? (Effectiveness needs to be considered in terms of the cellular mechanism of the drug, the dose regimen used, the case definition on which the drug and regimen are used, at what timing in the course of the disease, and in comparison to other possible drugs.) And will the drug use lead to a food safety issue? (Food safety issues might arise because a drug which is unsafe in humans is used or because an inappropriate withdrawal time is applied.)

On the other hand, if the outcome of extralabel drug use is compliance with laws and regulations, then it is important to know whether a particular drug use is as labeled or extralabel. Extralabel use, which is any use not included on the label (e.g., dose, route, frequency, duration, indication, production class of the animal, or species of animal), requires particular labeling under federal law, requires veterinary oversight that rises to the level of the VCPR or veterinary-client-patient relationship as defined in the federal regulation related to extralabel use (AMDUCA and its regulations as codified in 21 CFR 530), and is prohibited under particular circumstances, such as in feed, in the absence of veterinary direction, or for production purposes. In addition, extralabel (or label) drug use that results in a violative residue or residue higher than a tolerance or safe level is by definition illegal. An important caveat to extralabel use in a production class not included on the label is that FSIS inspectors are now interpreting tolerances for drugs in 1 production class of animals to NOT apply to other production classes. In other words, if a drug is approved in beef cattle and is used in dairy cattle, the tolerance no longer applies, which means in effect that the tolerance is zero.

The comparison of desired outcome, (1) effective drug use and safe animal product vs. (2) compliance, perhaps becomes clear when considering examples. For example, consider the use of metronidazole as a treatment for trichomoniasis in bulls: effectiveness is possible, at least based on some older studies in the peer-reviewed literature. However, metronidazole has been shown to

be carcinogenic or teratogenic in laboratory animals, so the ethical veterinarian would consider it inappropriate for use in an animal that will enter the food supply. The veterinarian who focuses on compliance might avoid metronidazole simply because it is declared to be illegal in AMDUCA. However, the compliance-based approach could lead to the decision to use metronidazole because the likelihood of detection at harvest might be low or because the veterinarian expects the animal to stay in the herd for many years. The compliance based approach may lead to risk-benefit analysis about getting caught rather than a focus on overall drug efficacy and food safety. And the compliance based approach may backfire when the consuming public learns of the misuse.

Perhaps the comparison of the 2 approaches is pedantic and philosophical, but being in a profession, veterinarians are obligated to uphold ethical standards, not just legal ones. I would argue that targeting an outcome of effective and safe (for animal and food supply) will result in better decision-making and more productive conversations with all stakeholders, including consumers. In point of fact, it could easily be argued that our responsibility as veterinarians is to keep both outcomes in mind. Perhaps a better question might be: which one is more successful at motivating all those involved in animal production to do the right thing, and which one is more successful in actually creating the environment on farms necessary to keep animals healthy and keep the food supply safe? That is a question veterinarians must answer for themselves, and a question that requires consideration of the veterinarian’s role on the farm.

### Veterinary Oversight

When contemplated drug use is extralabel, federal law mandates a VCPR. But in the event that particular drug uses are either on-label, or over-the-counter (OTC), what should the veterinarian’s role be? Is veterinary involvement important to effective and safe (to animals and humans) drug use on farms regardless of the drug type? As veterinarians, we are aware of what our knowledge base is (or what it can be, as a part of a commitment to lifelong learning), so we would argue that veterinary involvement in fact results in more appropriate drug use. To use and recommend the use of drugs, veterinarians should know how to read drug labels (particularly for prescription drugs, which are defined by the inability to provide instructions for laypersons); how to evaluate drug information (such as critical appraisal of peer-reviewed scientific literature); and what drugs do and how to evaluate the risks and benefits of a particular drug (e.g., adverse effects vs. likely effectiveness in animal populations). In addition, as evidenced through completion of jurisprudence training in veterinary school, federal accreditation, and

continuing education, veterinarians should be aware of the legal framework for safe and effective drug use. The totality of this knowledge base and critical thinking skills are what veterinarians bring to the table in drug decision-making and drug use oversight, whether the use is OTC or prescription, or as labeled or extralabel.

One example of an approach that perhaps provides some of both philosophical approaches, a compliance mind-set in combination with the professional considerations of effectiveness and animal and human safety, is the Wisconsin Veterinary Medical Association HACCP approach to proper drug use. This approach emphasizes the processes to have in place to provide safe and effective drug use, although the importance of considering efficacy of drugs is not described in detail in the WVMA materials. It would be inferred to be part of veterinary oversight and development of safe and effective protocols, obviously not a trivial matter. It is true that the major goal of the WVMA program is to reduce residues, which means there is considerable focus on regulatory compliance. However, it does provide a systematic way to review and discuss drug use, and using the HACCP approach highlights the high risk uses.

One high-risk use that demands discussion is any use of drugs in animals that are at risk of being culled. The compliance-based approach of drug decision-making described above might lead to the use of short-withdrawal-time products in animals at risk of being culled. The philosophical and ethical approach, however, is actually more likely to result in compliance: an animal at risk of being culled is likely to be euthanized on the farm rather than being exposed to last-ditch treatment efforts. In fact, the last-ditch treatment effort is likely to backfire,

since the ill cow is more likely to be targeted for residue testing at harvest, and the disposition of the drug in such an animal may be affected by her health status, thereby challenging the assumptions that went into the drug study that defined the labeled withdrawal time.

### Scenarios for Consideration

Here are a few scenarios for which veterinarians might consider the legal and ethical implications; for most of them, there is not a black-and-white answer, depending on the interpretation of regulations, the needs of the client, the will of the producer, and the will of the consumer. However, contemplating ahead of time as to how one might respond to a request for therapeutics or consultation in these cases may lead to better and more informed choices, which result in healthier animals and a safer food supply. Would you come to a different conclusion if the approach was compliance-based or professional/ethical?

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