Using FDA Approved Medications: Common Scenarios

Mike Apley[i], Virginia Fajt[ii], and Dee Griffin[iii]

The FDA approves drug labels with specific disease indications, animal classes, routes of administration, durations of therapy, and doses. Deviation from these label inclusions could potentially cause lack of effectiveness for the disease being treated, toxicity to the animals, or a violative residue in food harvested from the animal. The drug withdrawal time, established by the FDA when the medication was approved, is based on the physiologic clearance data specifically at the dose, location, route, frequency, and duration regimen approved on the label.

Prior to publication of the Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations in 1996, it was illegal to use a drug in an extralabel manner (any manner other than specified on the label). This law and resulting regulations enabled licensed veterinarians to adjust the use (extra label drug use – ELDU) of an FDA approved drug other than as labeled when the health and well-being of that animal or group of animals is threatened. ELDU shall not be considered if the purpose is for growth promotion, reproductive performance, or alteration of cost of therapy. This seems very straightforward, BUT, there is one very important point in the law. Even if the rationale for ELDU is reasonable, **ELDU must not lead to a violative drug residue**.

Points in the law that prevent unwanted consequences from ELDU include strictly forbidding ELDU without veterinary involvement and requiring there be a "valid veterinary client patient relationship" (VCPR) when ELDU is considered by a veterinarian. The FDA considers a valid VCPR to exist when: a) the licensed veterinarian has assumed clinical responsibility for the animals and the owner of the animals has agreed to follow the veterinarian's instructions; b) the veterinarian has sufficient direct knowledge of the animals condition and their care; and c) the veterinarian is available for follow-up evaluation. Additional conditions that must be met before ELDU may be legally considered are: a careful diagnosis is made by an attending veterinarian; there is no marketable drug specifically labeled to treat the condition diagnosed, or treatment at the dosage recommended by the labeling was found clinically ineffective; assurance that identity of the treated animal(s) is carefully maintained; and a significantly extended drug withdrawal is assigned to the animal(s) so that no violative residue occurs. If the individual animal cannot be identified for the extended withdrawal time, then the extended withdrawal time must be applied to the entire group.

Some examples of ELDU of injectable drugs that can cause violative residues are using penicillin G at a higher than labeled dose, administering Excede® (ceftiofur crystalline acid) by an unapproved route, and administering flunixin meglumine (e.g., Banamine®) by an unapproved route. Penicillin G is available over the counter (non-prescription), and the label dose is one CC per hundred pounds of body weight, at no more than 10 CCs per injection site. Only a licensed veterinarian can make the decision that the medically appropriate dose is five CCs per hundred pounds and as described above, the veterinarian must add a prescription label to the drug. When this altered dose is used, the necessary slaughter withdrawal time must be changed from the withdrawal time on the label by the prescribing veterinarian. If there is not sufficient information to establish this slaughter withdrawal time, then the animal may not enter the food chain.

Excede administered subcutaneously (SQ) in the neck region instead of the label directed middle portion of the back of the ear or base of ear locations changes the disposition of the drug. The potential for a violative residue at the injection site increases the required withdrawal time well beyond the label withdrawal time of 13 days. Altering the route of administration for flunixin meglumine from intravenous (IV) to subcutaneously (SC) or intramuscularly (IM) because of convenience rather than using the approved IV route of administration is very likely to result in a violative residue. This medication, when used SC or IM, causes a great deal of tissue damage at the injection site and violative residues have been documented by the FDA to occur in cattle beyond the four day withdrawal time the FDA requires for IV use of the medication.

The rules relating to AMDUCA and ELDU for feed additives drugs are different; ELDU of feed additives is prohibited. One scenario that needs clarification relates to "AM/PM" (feeding one drug in the ration in the morning or AM and feeding a different drug in the afternoon or PM) feeding of rations containing feed additives that are not approved by the FDA to be fed in combination with each other. **Feed additives must be used only according to the label instruction; concurrent feeding of drugs not approved to be fed together to cattle violates federal regulations and is illegal**. The AMDUCA regulations do not permit extralabel use of drugs that are administered in feed; not even a veterinarian may legally prescribe or use drugs in feed in an extralabel manner. Therefore, the FDA

believes the “AM/PM” use of feed additives which are not approved to be fed in combination is inconsistent with the intended conditions of use of combination products. These products are explicitly intended to be fed as the sole ration. Therefore, one feed additive should be discontinued prior to another feed additive being introduced to the animal.

The following combinations of feed additives are examples of those that have been approved by the FDA for concurrent use when fed according to label dosage and use:

- Bovatec® (lasalocid) + Aureomycin® (chlortetracycline)
- Deccox® (decoquinate) + Aureomycin® (chlortetracycline)
- Rumensin® (monensin) + Tylan® (tylosin) + Deccox® (decoquinate).
- Rumensin® (monensin) + Tylan® (tylosin) + MGA® (melengestrol acetate).

Any other unapproved combinations of these ionophores and feed antibiotics are prohibited. Label directions on feed additives must be followed exactly, including for example disease indication, drug concentration in the feed, frequency and duration of administration, and withdrawal times.

Let’s consider an example to clarify. A group of cattle are on a ration with approved levels of Rumensin® and Tylan®. If these cattle develop a health condition for which the veterinarian recommends feeding chlortetracycline (CTC) for 5 days, the ration containing Rumensin®/Tylan® must be stopped prior to beginning the ration containing CTC. This includes CTC pellets. A pelleted feed additive cannot be top dressed over a ration containing a medication for which it combination feeding has not been approved. Once the CTC therapy is completed, feed containing Rumensin®/Tylan® can be fed again. Combinations of drugs in feed are approved by the FDA to verify that no interactions between the drugs will occur in the animal. Therefore, feeding rations containing non-approved combinations is illegal.

Producers are required by law to make all feed additive use records available to an FDA inspector upon request. A good management practice is to include the exact times rations containing a feed additive were removed and the exact time a ration containing a different feed additive was delivered to the cattle. This helps the FDA inspector appreciate the diligence practiced to prevent cross contamination of rations containing feed additives not approved to be fed in combination.

The above discussion attempts to clarify some of the legal requirements for ELDU by producers and veterinarians. It should be clear that the rules are different for injectable drugs and drugs administered in the feed. Questions about the legal use of over the counter and prescription drugs can be addressed by your veterinarian.

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[i] Mike Apley, Veterinarian & Professor of Clinical Sciences, College of Veterinary Medicine, Kansas State University
[ii] Virginia Fajt, Veterinarian & Clinical Assistant Professor, Texas A&M University and Chair of the Committee on Pharmaceutical and Biologic Issues of the American Association of Bovine Practitioners
[iii] Dee Griffin, Veterinarian, University of Nebraska – Lincoln, Great Plains Veterinary Educational Center