CLINICAL APPLICATION
Watch the Inert Ingredients

A practitioner called a veterinary referral hospital with a question regarding the possibility of an ear medication causing signs associated with ototoxicity (*oto*, meaning ear, and *toxic*, meaning poisonous). A young puppy was showing signs of circling (walking around in circles), head tilting to one side, and nystagmus (rapid eye movement back and forth). These signs were consistent with inflammation, disease, or damage to the inner ear, where the organs of balance are located. The practitioner knew that certain ear medications had a reputation for producing ototoxicosis, but she also knew that the otic (ear) preparation that she had prescribed did not have any of those ingredients listed on the active ingredient label. However, although the active ingredient was not associated with ototoxicity, the solvent added to the otic preparation to soften the ear wax had occasionally been reported as producing an ototoxicity exhibiting these signs. The otic medication was stopped and the puppy recovered within 12 hours.

What should be learned from this situation: Reactions to medications can come from the additives, not just the main ingredient. For example, intravenous drugs dissolved in propylene glycol appear to have a much greater potential to produce side effects if given rapidly than the same drug dissolved in water and given just as rapidly.

Therefore this section of the drug listing can be important in attempting to identify causes of an adverse drug reaction.

The *indications* section of the drug listing tells for what purposes the drug may be used. Indications are the specific, FDA-approved uses for the drug. When the FDA approves a drug for use in veterinary medicine, it is for a specific species (e.g., dog, cat, cattle), for a specific disease, and at a specific dose. Even though the drug may have other effective medical uses, the specific indications for which the drug has been tested and approved ar
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CLINICAL APPLICATION
Extra-Label Drug Use

The Food and Drug Administration (FDA) has the responsibility of ensuring the safety and effectiveness of all drugs and is charged with monitoring the safety of the food supply. This tremendous responsibility, as defined by the Federal Food, Drug, and Cosmetics Act, places the FDA in the role of watchdog over the ways veterinary drugs are used. Section 512 of the Act states that an animal drug is considered unsafe unless it has been approved and the intended use of the drug conforms to that approval. Alteration of any of the following from what is described and approved on the drug label is considered extra-label use:

- Use in a species not listed
- Use for an indication (disease or condition) not listed
- Use of a different dosage
- Use of a different frequency of administration
- Use of a different route of administration
- Deviation from labeled withdrawal time (time from last administration of the drug until the animal or the animal's products can be safely taken to market)

Because the FDA is charged with safety of the human food supply, and drug residues in meat, egg, milk, and food products are an adulteration of the food, the act is primarily directed toward the use of drugs in food animals (e.g., cattle, sheep). Veterinarians are often limited by what drugs they can use to treat food animal species because of the concern over drug residues in human food products and the tight restrictions on extra-label use.

In 1994 Congress passed the Animal Medicinal Drug Use Clarification Act (AMDUCA) which gave veterinarians the authority to use approved animal drugs in an extra-label manner. In other words, a drug approved for use in cattle for respiratory infection could be used for respiratory disease in sheep if the "health of the animal is threatened, or suffering or death may result from failure to treat." In addition, extra-label use is only valid and legal when the following criteria are met:

- No approved drug exists that is specifically labeled to treat the condition diagnosed, or the approved drug at the dosage on the label has been found by the veterinarian to be clinically ineffective in the animals to be treated.
- A careful medical diagnosis is made by the attending veterinarian within the context of a valid veterinarian-client-patient relationship (VCPR). A valid VCPR according to the American Veterinarian Medical Association Membership Directory and Resource Manual exists when the veterinarian has assumed the responsibility for making clinical judgments, the client has agreed to follow the veterinarian's instruction, the veterinarian has sufficient knowledge of the animal to make a preliminary diagnosis, and the veterinarian is readily available for follow-up evaluation in the event of an adverse reaction or treatment failure.
- Procedures are instituted to ensure that the identity of the treated animal is carefully maintained.
- A significantly extended period is assigned for drug withdrawal before marketing meat, milk, or eggs from treated animals, and steps are taken to ensure that the assigned time frames are met and that no illegal residues occur.
- The prescribed or dispensed extra-label drugs bear labeling information that is adequate to ensure the safe and proper use of the product. This would include the following:
  - Name and address of the prescribing veterinarian
  - The active ingredients
  - Animal the drug is to be used on (identification, class, or species)
  - Dosage, frequency, route of administration, and duration of therapy
  - Any cautionary statements specified by the veterinarian
  - Veterinarian's specified withdrawal/discard time for meat, milk, eggs, or food
  - Products derived from the treated animals

Veterinary professionals have an obligation to the public to support the veterinarian's and FDA's efforts to ensure that extra-label drugs are used in a safe and responsible manner. Veterinary technicians may have to explain or defend this policy or may be challenged to bend the rules "just this once." Veterinary technicians must understand both the intent of the regulations and the physiologic reasons that form the rationale behind appropriate extra-label drug use.

For example, stomach upset caused by aspirin is considered a mild side effect and is included under precautions. The veterinarian must then use clinical judgment to decide whether the benefits of the drug outweigh the potential side effect. By listing the precautions (including even mild side effects), the drug manufacturer has legally informed the veterinarian of the potential side effects or adverse reactions and placed the responsibility for administering the drug on the veterinary professional.

Warnings are more serious or frequent side effects than those found in the precautions section, such as the potential for hallucinations in an aspirin-sensitive person taking aspirin compounds. Because many of the adverse reactions in the warnings section are potentially life threatening, veterinary professionals have a moral and ethical obligation to thoroughly understand the key points of warnings and to inform the client or owner of the potential problems that may arise. Drugs that contain warnings can still be given if the potential benefit, in the judgment of the attending veterinarian, outweighs the risk.

Contraindications are circumstances in which the drug should not be used. For example, giving penicillin to an animal or person who has severe and life-threatening allergic reactions to penicillin is contraindicated. The potential for a hypersensitivity reaction in a patient is a contraindication condition for penicillin. Failure to heed a known contraindication for a drug, with subsequent death of the veterinary patient because of administration, could constitute malpractice.

When applicable, information on a drug overdose or overdosage is also supplied in the drug inserts and drug information bulletins. Overdose can occur from a dose miscalculation or when illness changes the normal physiologic state, causing an administration of a correct dose of drug to accumulate and produce signs

CLINICAL APPLICATION
The Long Regulatory Arm of the Law

In 1997 the U.S. District Court convicted a livestock dealer for providing false information to the U.S. government and for introducing adulterated food. The United States Department of Agriculture Food Safety and Inspection Service reported more than 50 instances of animals offered for slaughter for human food that contained illegal levels of antibiotics and other drugs. Although the plea agreement resulted in tougher regulation for this livestock producer, the potential penalty for providing false information to the U.S. government is imprisonment for 5 years, a fine of $250,000, and a 3-year period of supervised release. The maximal penalty for introduction of adulterated food into interstate commerce is imprisonment for 1 year, a fine of $100,000, and a 1-year period of supervised release.[1]

A veterinarian was sentenced in U.S. District Court to 8 months in federal prison and fined $15,000 after pleading guilty to a charge that he conspired to smuggle an illegal substance into the United States. The veterinarian admitted to selling more than $75,000 worth of clenbuterol to six customers whose children used the beta-agonist drug to improve the appearance of several show animals from 1986 to 1994. Clenbuterol has been used illegally to increase muscle mass and decrease fat deposition, giving show livestock an appearance that is an advantage in showing competition. The veterinarian was dispensing the medication to animals that he knew would be slaughtered for food, thus potentially introducing drug residues into human food sources.[2] Clenbuterol leaves a drug residue that cannot be eliminated by cooking and if eaten can potentially be dangerous. What should be learned from this situation: In these cases the veterinarian and livestock producer had been doing this illegal practice for several years and appeared to be complacent in their concern for the potential impact on the food human beings eat. Veterinary professionals can help keep this from happening by following the rules and regulations for the use of animal drugs in veterinary patients.