FARAD Digest

Extralabel drug use in wildlife and game animals

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From a food safety point of view, any animal that has the potential to be consumed by humans is considered a food-producing animal; therefore, the regulations pertaining to ELDU in food-producing animals should be followed. This applies to wildlife species that may be free ranging or captive raised and consumed by humans, such as cervids, game birds, and marine mammals as well as species treated in wildlife rescue and rehabilitation centers, because those animals have the potential to be anesthetized, treated for injuries or illnesses, and released back into their native habitats following anesthesia or drug administration.

For the purpose of this digest, wildlife or game animals will refer to free-ranging nondomesticated mammals, reptiles, and bird species as well as animals that are confined or farm raised and subsequently hunted for personal consumption or slaughtered for commercial purposes and thus are considered food-producing animals. The FDA defines a game animal as any animal from which food products may be derived that is not classified as livestock (eg, cattle, sheep, swine, goats, horses, mules, or other equids), poultry, or fish.[1,2]

Although a large proportion of game species are hunted for personal consumption, a portion of that population does enter the commercial food industry. The number of game animals entering the commercial food sector has changed over the last several years. For example, the number of bison in production and the sale of bison products decreased by 18.22% and

8.83%, respectively, from 2007 to 2012.[3] The number of game birds in production also fluctuated between 2007 and 2012,[3] with the number in production increasing for some species and decreasing for others. Despite those fluctuations, it is not unusual for FARAD to receive requests for WDI recommendations following ELDU in wildlife species. The purpose of this digest is to provide veterinarians with summary information regarding drug use in wildlife species with the ultimate goal of safeguarding the human food chain because the pharmaceutical treatment history is generally unknown for free-ranging animals.

Best Practices and Responsibility for Drug Residue Avoidance

Veterinarians and producers play an important role in preventing products tainted with drug residues from entering the human food chain through sound record keeping and judicious and responsible drug storage and administration. Drug residue avoidance is widely practiced in domestic food animal medicine and for commercially farmed nondomestic species. However, drug residue avoidance for free-ranging wildlife that are hunted or rehabilitated could benefit from broader recognition of best practices. Residues refer to the presence of drugs, drug metabolites, contaminants, or pesticides in meat, milk, eggs, and other edible products. The presence of residues in food products can cause reactions in consumers who are allergic or sensitive to those substances and can be fatal.[4] According to the FDA, failure to observe drug label directions and WDTs, human negligence, and poor food manufacturing practices are the primary causes of illegal drug residues in animal-derived food products in the United States.[5] Veterinary oversight is key for the prevention of residue violations. Hunted wildlife are considered minor food-producing species and are subject to the regulations that govern ELDU in food animals.

ABBREVIATIONS

CPG	Compliance policy guide
DEA	Drug Enforcement Agency
ELDU	Extralabel drug use
FARAD	Food Animal Residue Avoidance and Depletion Program
FSIS	Food Safety Inspection Service
VCPR	Veterinarian-client-patient relationship
WDI	Withdrawal interval
WDT	Withdrawal time

For wild animals that are treated with drugs, some states require withdrawal periods or waiting times prior to the respective hunting seasons for those animals. Those policies exist because of the availability of only minimal drug elimination data for wild animals and concerns about public health. The wildlife management agency in the state where the animal will be released should be consulted for more information regarding this topic.

It is imperative that FDA-approved WDTs or scientifically based WDIs are adhered to when drugs are administered to farmed species. This concept also applies to wild animals that are being rehabilitated and require drug administration and to free-ranging animals that are anesthetized for various reasons. Drugs are administered to wild and free-ranging animals by various methods such as remote delivery devices (eg, darts), feed, and water or by more traditional methods during hands-on treatments or procedures. Because those animals are often released back into their native habitats after rehabilitation or anesthesia recovery, it is possible that they could be subsequently harvested by hunters and used for human consumption. Owing to the unknown fate of wildlife species, it is best that such animals be considered food-producing animals and treated accordingly. This means that WDTs and WDIs need to be adhered to following drug administration and that animals should not be anesthetized or treated and released during the hunting season for that species. Additionally, the veterinarian of record is responsible for ensuring, to the best of his or her ability, that a treated animal does not enter the human food chain until it is safe to be consumed. Identification is recommended for any animal that could potentially enter the human food chain while it still has violative drug residues in edible tissues. Suggestions for identifying a treated animal include the application of a tag or collar to the animal with a warning to not consume before a specific date or with a phone number to call before consuming. Complete records that include animal identification, information regarding the drug administered, and the person responsible for administering the drug should be maintained in case an animal is harvested prior to completion of the WDI and a hunter contacts the responsible party. The carcass and all edible products of animals that are harvested prior to completion of the required WDT or WDI should be disposed of in an appropriate manner and not used for human consumption.

Pharmacokinetic data are typically obtained from a small number of healthy animal subjects during the drug approval process, and published studies generally provide mean pharmacokinetic parameters, which form the basis for clinical drug use. However, the efficacy, metabolism, absorption, and elimination of drugs are dependent on many factors such as species, coadministration of other drugs, and patient body condition, disease state, diet, and age. Those factors need to be considered during determination of a sci-entifically based WDI, and extended withdrawal periods may be warranted in some cases.

Extralabel drug use in animals is allowed under conditions outlined in AMDUCA.[6] Briefly, the drug administered must be approved by the FDA and used for therapeutic rather than production purposes on the lawful written or oral order of a licensed veterinarian within the context of a valid VCPR. If the animal that receives a drug in an extralabel manner has the potential to enter the human food chain, the veterinarian of record must also identify the treated animal, establish an appropriate and substantially extended WDI, and ensure that the established WDI is adhered to so that violative residues do not occur.

In the United States, legal ELDU is defined as the use of a drug in any manner other than that described on the FDA-approved label but within the conditions established by AMDUCA[6] and FDA regulations. This includes, but is not limited to, changes in dose, frequency of administration, administration route, species, or indication. When an FDA-approved drug is administered to a food-producing animal and a tolerance for that drug has not been established in that species, detection of any residue of that drug in the animal at the time of slaughter is a violation. The tolerance of a drug is the maximum concentration of the marker residue (ie, the drug or one of its metabolites) that is deemed safe for human consumption.

The FDA and USDA FSIS are responsible for ensuring that edible products entering the human food chain are free of contaminants and safe to consume. If a veterinarian prescribes, administers, or dispenses a drug and does not take measures to ensure that animals treated with that drug do not enter the human food chain while they still have violative tissue drug residues, the veterinarian may be held responsible for the violation. Regardless of the source of a violation, the FDA and FSIS can hold "any individual in the production and marketing chain who can be shown to have caused" the violation "by an act of commission or omission" accountable for any prohibited residues or contaminants in edible animal products.[5]

Game animals are classified as nonamenable species and undergo voluntary inspection by FSIS in accordance with the Agriculture Marketing Act.[7,8] On a yearly basis, the FSIS publishes the National Residue Program Residue Sampling Plan in the *Blue Book*,[9] and the National Residue Program Residue Sample results from previous years in the *Red Book*.[10] Both of those books are targeted primarily toward major food-producing species, but they can be used as guides for potential residue testing of edible products derived from game animals. During inspection, an inspector can warrant testing of any carcass on the basis of their professional judgement and require analysis of that carcass for FDA-approved and unapproved drugs, pesticides, hormones, and environmental contaminants.[11] The *Blue Book*[9] and *Red Book*[10] are both available online.

Owing to the minimal regulatory oversight for products derived from game animals, veterinarians are encouraged to take responsibility and educate clients about best practices to avoid drug residues in edible products destined for human consumption. Because there are few FDA-approved drugs and drug tolerances established for game species, most drugs are administered to such animals in an extralabel manner, and the detection of any drug residues in edible products derived from those animals is considered a violation.

FDA-Approved Drugs for Wildlife

Wildlife are susceptible to many diseases and parasites, especially during periods of extended rehabilitation or when large numbers of animals are maintained or confined in a fairly small area. The drugs approved for use in wildlife by the FDA, although few in number, have been summarized **(Table 1)**. Details regarding use of FDA-approved drugs and established tolerances for those drugs in mammalian and avian wildlife species can be found on the Animal Drugs@ FDA,[12] FARAD VetGRAM,[13] and Minor Use Animal Drug[14] websites.

ELDU in Captive and Free-Ranging Wildlife

Given the paucity of drugs with FDA approval for use in wildlife, ELDU is often the only alternative for treating injured or diseased wild animals and is legal as long as the stipulations outlined by AMDUCA are followed. However, drugs that are restricted or prohibited from use in food animals[15] **(Table 2)** should not be administered to wild animals that might be subsequently used for human consumption. Additionally, for wildlife, ELDU is permissible only when the treated animal or animals can be kept in captivity or otherwise identified as not safe for human consumption during the WDI.

Administration of an FDA-approved drug to a species that is not listed on the label is considered ELDU, and only veterinarians can prescribe use of FDA-approved products in an extralabel manner. It is illegal for producers, wildlife rehabilitators, or biologists to use a prescription or over-the-counter medication in an extralabel manner unless those drugs are prescribed or dispensed by a licensed veterinarian within the context of a valid VCPR.

When considering the treatment of a large number of nondomestic animals, it is important to remember that AMDUCA stipulates that ELDU is permissible only for therapeutic purposes. Prophylaxis or metaphylaxis may be allowed, but the prescribing veterinarian should be prepared to provide evidence-based documentation of historical flock or herd diseases and associated morbidity and mortality rates. Some states have practice acts that define the regulations regarding such documentation.

Many FDA-approved drugs are available only by prescription and require veterinary supervision. Non-

Table 1—Summary of products approved by the FDA for use in wildlife species as of September 2018.

Species	No. of FDA-approved products	Active ingredient (NADA No.)
Game birds	19	Iodinated casein (005–633)
		Amprolium (012–350)
		Novobiocin (012–375)
		Thiabendazole (015–875)
		Monensin sodium (038–878, 130–736)
		Ormetroprim-sulfadimethoxine (040–209)
		Bacitracin methylenedisalicylate (046–592, 065–470, 141–137)
		Bacitracin zinc (046–920, 065–313, 098–452, 200–223)
		Chlortetracycline (200–510)
		Chlortetracycline (calcium) (048–761)
		Lasalocid sodium (096–298)
		Salinomycin (128–686, 200–075)
Cervids	14	Ivermectin (128–409, 200–429, 200–437, 200–447, 200–228)
		Xylazine hydrochloride (200–529, 200–088, 200–139, 139–236, 047–956)
		Yohimbine hydrochloride (140–874)
		Naltrexone hydrochloride (141–074)
		Gelatin–sodium chloride (006–281)
Bison	5	Ivermectin (128–409, 200–228, 200–429, 200–437, 200–447)
Rabbits	2	Sulfaquinoxaline (006–391)
		Lasalocid sodium (096–298)
Weasels and mink	2	Melatonin (140–846)
		Novobiocin (012–375)
Bears	1	Fenbendazole (121–473)
Feral swine	1	Fenbendazole (131–675)
Bighorn sheep and goats	1	Fenbendazole (131–675)
Foxes	1	Ivermectin (128–409)
Wild felids	1	Fenbendazole (121–473)
Unspecified wildlife	1	Diprenorphine hydrochloride–etorphine hydrochloride (047–870)

NADA = New animal drug application.

Table 2—Drugs or drug classes prohibited from ELDU or with only restricted ELDU permissible in food-producing animals.

Drugs or drug classes prohibited from ELDU in food-producing animals	Drugs or drug classes with only restricted ELDU permissible in food-producing animals
Chloramphenicol	Adamantanes
Clenbuterol	Neuraminidase inhibitors
Diethylstilbesterol (DES)	Cephalosporins (not including cephapirin)
Fluoroquinolones	Gentian violet
Glycopeptides, including vancomycin	Phenylbutazone
Nitroimidazoles, including dimetridazole, ipronidazole, and metronidazole	Sulfonamides
Nitrofurans, including furazolidone and nitrofurazone	
Indexed drugs	

For the most up-to-date information on drugs prohibited or restricted from ELDU in food-producing animals, consult the most recent Code of Federal Regulations, Title 21, Section 530.41.[15]

veterinarians can legally administer prescription and over-the-counter drugs in an extralabel manner if a valid VCPR has been established and the veterinarian has prescribed the medication. The veterinarian does not have to be physically present for drug administration as long as the veterinarian of record can be readily contacted, is directly involved in the planning process (ie, diagnosis and development of the treatment plan, including drug dosages, schedule, and residue prevention procedures) for the animal or animals being treated, and ELDU is documented.

Controlled Substances Used in Game Animals

Some anesthetic agents and drugs used for immobilization of wildlife are controlled substances. In the United States, the DEA classifies controlled substances as schedule 1 to 5 drugs, and the regulations regarding controlled substances are outlined in the US Code of Federal Regulations Title 21 part 1301.75[16] and the Controlled Substances Act.[17]

Veterinarians and biologists must obtain a DEA registration number to purchase controlled substances through veterinary product distributors. Even though biologists can legally obtain controlled substances, they cannot administer them to animals without veterinary guidance because controlled substances are available only by prescription and must be used by or on the order of a licensed veterinarian within the context of a valid VCPR. As long as a valid VCPR has been established, the veterinarian of record does not have to be physically present when the drugs are administered; however, the veterinarian of record does need to be directly involved in determining the drug and dosage administered. From a regulatory standpoint, biologists are typically classified as clients and wild animals are classified as patients.[18] This is advantageous for biologists who work in isolated or remote areas because it allows them to proceed with their work without a veterinarian having to be physically present during drug administration to animals. The definition of a valid VCPR varies among states. Therefore, FARAD recommends that veterinarians check

with the veterinary board and natural resource and wildlife departments of the state in which biologists will be working to ascertain exactly what constitutes a valid VCPR in that state and determine whether biologists can administer prescription drugs to animals without a veterinarian being physically present.

Additionally, most states have a board of pharmacy with their own set of regulations that must be followed. Those regulations may be more restrictive than the FDA and DEA in terms of the acquisition of certain drugs and controlled substances. For further information and clarification regarding those regulations, FARAD recommends that veterinarians contact the board of pharmacy for the particular state where the work is to be performed.

ELDU of Medicated Feeds in Wildlife

The FDA prohibits extralabel use of medicated feeds in major food-producing species (eg, cattle, pigs, chickens, and turkeys) but not minor species. Guidelines for extralabel use of medicated feeds in minor species are outlined in CPG 615.115.[19] That CPG does not establish legally enforceable responsibilities, but it does provide guidance to FDA field inspectors regarding when to take regulatory action against veterinarians or producers following the discovery of extralabel use of medicated feeds to minor food-producing species.[19] For minor food-producing species that are farmed or maintained in confinement, extralabel use of medicated feeds will generally not result in regulatory action as long as all AMDUCA stipulations and guidelines outlined by CPG 615.115 are met. Extralabel use of medicated feeds in free-ranging wildlife is not permitted under CPG 615.115.[19] Further information regarding extralabel use of medicated feeds in farmed minor species is available in a previous FARAD Digest.[20]

Index of Legally Marketed Unapproved New Animal Drugs

The FDA maintains an Index of Legally Marketed Unapproved New Animal Drugs for Minor Species,

often referred to simply as The Index.[21] Drugs that appear on The Index are referred to as indexed drugs. Contrary to FDA-approved drugs, indexed drugs undergo an alternate FDA review procedure to confirm their safety and effectiveness.[22] In some cases, drugs for minor species are intended for uses that are not conducive to the standard drug approval process. The indexing process is helpful to individuals who treat animals or classes of animals that represent markets that are too small to support the costs associated with the standard FDA drug approval process. Indexed drugs are often intended for use in rare or diverse species that cannot be reasonably acquired or maintained in sufficient numbers for traditional safety and efficacy studies. The indexing process is a quicker and more economical alternative than the traditional FDA drug approval process for companies to acquire legal marketing status for products intended for use in non–food-producing minor species and the early life stages of food-producing minor species.[21]

Although indexed drugs are not technically approved by the FDA, they can be legally marketed in the United States. However, ELDU of indexed drugs is prohibited in all animal species. A comprehensive list of indexed animal drugs can be found on the FDA website.[23]

Compounded Drugs

Many wildlife veterinarians often use compounded anesthetics, tranquilizers, antagonists, and other unique drugs because they need a higher concentration of a drug than that in commercially available formulations, a product has only limited availability or is unavailable owing to its discontinuation by manufacturers, or there is a need for multidose vials. The FDA defines compounding as any manipulation of a drug beyond what is included on the FDA-approved label, and a compounded drug is typically viewed as an unapproved new drug.[24-26] Compounding can include activities such as mixing 2 or more FDA-approved drugs together into a single dosing form (eg, syringe or dart), as is commonly done when combining anesthetic drugs used to capture wildlife species. It can also include altering the physical form of a drug such as crushing or dissolving tablets or adding flavoring prior to oral administration. Compounding also includes the creation of drug formulations from bulk chemical active ingredients and inactive ingredients such as flavors, binders, fillers, diluents, and suspending agents. However, AMDUCA prohibits the administration of drugs compounded from bulk substances.[26]

The use of compounded drugs in food-producing animals is discouraged by FARAD because compounded products do not undergo the same quality assurance testing as commercially manufactured medications, and the efficacy and safety of compounded drugs can be questionable. Minor changes in additives or their concentrations can modify the depletion profile for a drug, even at low concentrations, thereby altering the WDI. Pharmacokinetic data generally do not exist for compounded drugs, which makes it difficult and often impossible to calculate a scientifically based WDI.

Compounded drugs from FDA-approved products can be used to treat food-producing animals as long as the requirements of AMDUCA[6] and legal compounding[25] are met. Further recommendations regarding the use of compounded drugs in food-producing animals can be found on the FARAD website.[26] At the time this digest was published, the FDA had not finalized a CPG for compounding animal drugs, and until a final guidance has been issued, the FDA will assess each case of animal drug compounding brought to its attention individually to determine whether it was lawful or unlawful.[27]

In regard to free-ranging wildlife, there are circumstances when mixing (compounding) injectable anesthetics together in a syringe or dart for administration is necessary from a safety perspective. If a compounded mixture is administered to a food-producing species, it is recommended that treated animals be identified with an ear or neck tag that instructs readers to not consume or to call a provided telephone number before consumption.[28]

Vaccines

Animal vaccines are considered veterinary biologics and are regulated by the USDA Center for Veterinary Biologics. Technically, AMDUCA applies to ELDU of only FDA-approved drugs; it does not apply to biologics. Therefore, extralabel use of vaccines is allowed at the discretion of the veterinarian of record.

Most vaccines marketed for food animals in the United States have a 21-day slaughter withdrawal period.[29] The recommended withdrawal period for vaccines can be affected by the adjuvant or antimicrobial preservatives. The USDA bases the recommended withdrawal periods for vaccines on gross and histologic evaluation of injection sites and other tissues (eg, nasal passages for intranasal vaccines) when indicated.[30] From a food safety point of view, if a vaccine label does not provide a milk withdrawal period and the label does not specifically state that the vaccine should not be administered to lactating animals, it can be assumed that there is no milk withdrawal period, and milk from vaccinated animals is safe for human consumption immediately after vaccination.[a]

Veterinarians are encouraged to contact FARAD if a vaccine containing an antimicrobial preservative is administered in an extralabel manner to a food-producing species. A WDI will be recommended provided FARAD has access to enough scientific data to formulate such a recommendation.

Hormone Implants

Extralabel administration of hormone implants, particularly to species not listed on the FDA-approved label, should be done with caution because interspe-

cies differences in anatomy and physiology may affect absorption and elimination of the active ingredients in the implants.[31]

Extralabel use of FDA-approved hormone implants in food-producing animals is allowed as long as the stipulations established by AMDUCA[6] are met. This means that ELDU of implants must be for therapeutic purposes only, and implants cannot be used in an extralabel manner for management purposes such as estrus synchronization, behavior modification, improvement of feed efficiency, or growth promotion. Whenever possible, implants should be implanted at the location described on the FDA-approved label to facilitate proper hormone absorption and clinical response. Most implants that contain a naturally occurring hormone have a 0-day WDT when administered in accordance with the FDA-approved label. However, when such an implant is administered to a game animal in an extralabel manner, an extended WDI would need to be observed to be in compliance with AMDUCA.

It is important that veterinarians are cognizant of whether individual implant products have been approved by the FDA or are classified as indexed drugs. For example, there is a subcutaneous hormone implant product that contains 4.7 mg of deslorelin/implant,[b] which is classified as an indexed drug and therefore cannot be administered in an extralabel manner because ELDU is permissible for only FDA-approved drugs. That implant can only be used in non–food-producing minor species or food-producing minor species in their early life stages in accordance with the label directions. Conversely, there is a subcutaneous implant product containing 2.1 mg of deslorelin acetate/implant,[c] which is approved by the FDA for induction of ovulation in horses. That product can be administered in an extralabel manner to any species for treatment of reproductive disorders or as a medical contraceptive[32]; however, an extended WDI would have to be observed if it was administered to a food-producing species.

Analgesics, Anesthetics, and Darts

Injectable anesthetics are commonly used to immobilize and anesthetize wildlife, but they tend to have a very narrow safety margin. Consequently, dose adjustment or titration might be necessary, and it is important that animals are closely monitored for adverse reactions.[33] Remote drug delivery systems vary on the basis of type of gun and needle used and can cause more muscle damage and necrosis than typical IM injections. Muscle damage and necrosis can cause prolonged or erratic drug elimination. Pharmacokinetic data for drugs administered by remote delivery systems are often lacking; therefore, the FARAD-recommended WDI for a drug administered by a remote delivery system is generally longer than that for the same drug administered IM with a hand-held syringe.

For wildlife species, FARAD frequently receives requests for recommended WDIs for analgesics, seda-

tives, and other injectable medications commonly used in anesthetic regimens such as butorphanol, xylazine, ketamine, tiletamine hydrochloride, and zolazepam hydrochloride. Another product for which FARAD often receives requests for WDI recommendations is a commercial formulation[d] containing both tiletamine and zolazepam, which is effective and commonly used for wildlife immobilization. There are limited pharmacokinetic data available for the tiletamine-zolazepam combination in bears. In 1 study,[34] tiletamine and zolazepam metabolites persisted for prolonged periods, especially in fat and muscle tissue, after administration of the combination product to polar bears. Conversely, the tiletamine-zolazepam combination was rapidly metabolized and eliminated following administration to black bears.[35] Pharmacokinetic data for the tiletamine-zolazepam combination in other wildlife species are lacking. Pharmacokinetic data are also lacking for administration of butorphanol to wildlife species. In cattle and many other domestic species, the plasma half-life of butorphanol is short and the volume of distribution is large, which suggest that low concentrations of the drug may accumulate in tissues and potentially result in residue violations.

Antagonist Drugs

In wildlife species, antagonist drugs are often used to reverse the effects of immobilization drugs. Use of antagonist drugs minimizes recovery time and the risk for tissue hypoperfusion and hypoxia.[36] They are also useful for patients that develop a life-threatening adverse reaction to an anesthetic.[36] Antagonist drugs act either as pharmacological antagonists or indirectly by physiologic antagonism.[36] Pharmacological antagonists compete for or alter the receptor sites for an agonist, which causes the agonist to be displaced, thereby reversing or preventing its effects.[37] Physiologic antagonists oppose the pharmacological effects of an agonist by acting on different receptors or distinct cellular pathways.[37,38] Although there are a fair number of antagonists labeled for use in animal species, FARAD has limited residue data for those agents. Prolonged agonist effects and renarcotization can result in metabolic problems or death if treated animals are not closely monitored.[39]

Nalorphine hydrochloride, a pharmacological antagonist, is approved by the FDA for use in dogs to facilitate recovery following opioid-induced anesthesia or respiratory and circulatory depression. Unfortunately, residue data for nalorphine in wildlife or food-animal species are not currently available. Naloxone, another pharmacological antagonist, is approved by the FDA to treat opioid overdose in humans but not in animals. The FARAD database contains limited naloxone tissue data in sheep[40,41] and swine[42] but has no tissue data for naloxone in any wildlife species.

Atipamezole is approved by the FDA for use in dogs to reverse the sedative effects of dexmedetomidine hydrochloride and medetomidine hydro-

chloride. Limited plasma data for atipamezole in food-animal species are available.[43–49] Tolazoline is a pharmacological antagonist approved by the FDA for use in horses to reverse the effects of xylazine. There are limited pharmacokinetic data for tolazoline in sheep[50] and cattle,[51] but pharmacokinetic data are lacking for wildlife species.

Neostigmine is a pharmacological antagonist approved by the FDA for use in sheep, swine, and beef and nonlactating dairy cattle as an antagonist for curare; it also has antagonistic effects against acetylcholine and gallamine.[37] Unfortunately, pharmacokinetic data for neostigmine in food-producing species are currently lacking.

Doxapram is a physiologic antagonist approved by the FDA for use in dogs, cats, and horses for reversal of the effects of xylazine, cyclohexylamine, and etorphine. Limited tissue residue data for doxapram are available for sheep[52] but not for any wildlife species. Owing to the limited tissue pharmacokinetic data currently available for most antagonist drugs, veterinarians are encouraged to contact FARAD for WDI recommendations following ELDU of such drugs in the event that new data becomes available.

Supplements

Products containing a combination of vitamin E and selenium are often used in wildlife species to alleviate or prevent capture myopathy, a poorly understood condition that commonly occurs in wildlife species during capture for identification and research purposes. Vitamin E and selenium deficiencies might be contributing factors in the development of rhabdomyolysis in animals, and animals deficient in vitamin E and selenium may be predisposed to capture myopathy.[53] That condition is most frequently observed in hooved wildlife but has also been reported in long-legged water birds, raptors, and marsupials.[54–56] Tissue residue data for vitamin E–selenium combination products are available for most domestic food-animal species,[57–60] but pharmacokinetic data for those products in wildlife species are currently unavailable.

In the United States, the manufacture of dietary supplements is not regulated; therefore, product quality is not assured. Dietary supplements might be contaminated with chemicals that could result in violative or harmful residues in food-producing species.

If dietary supplements are administered in accordance with the label directions and no withdrawal period is stated on the label, then no withdrawal period is required. However, if dietary supplements are administered in an extralabel manner, an extended WDI may be required.

Prohibited Drugs

In the United States, it is illegal for drugs that the FDA has prohibited or restricted from use in food animals[15] (Table 2) to be administered to any animal, domestic or wild, that could potentially enter the human food chain. Most of the prohibited drugs are medically important antimicrobials used in human medicine or have been shown to represent a risk to human health when consumed in products derived from treated animals. The adverse effects of and risks associated with prohibited drug residues are not considered to lessen over time such as between hunting seasons or following extended withdrawal periods. Drugs approved by the FDA for use in food-producing species should be used for the treatment of captive and free-ranging wildlife whenever possible.

Enrofloxacin is a fluoroquinolone, and it is one of the most common drugs for which FARAD receives requests for WDIs. The FDA expressly prohibits the ELDU of fluoroquinolones in all food-producing species, including captive and free-ranging wildlife.[15] Thus, enrofloxacin can be legally administered only in accordance with the FDA-approved label (ie, to swine for the treatment and control of respiratory disease at any age or for the control of colibacillosis in weaned pigs and to beef cattle and dairy cattle < 20 months old for the treatment and control of respiratory disease). In human medicine, fluoroquinolones are frequently used to treat bacterial infections that are resistant to other antimicrobials and life-threatening illnesses such as pneumonia caused by *Pseudomonas* spp. The prohibition of the use of fluoroquinolones in food-producing species was enacted in an effort to preserve the efficacy of that essential class of drugs in human patients.

To reiterate, in the United States, no drug (including enrofloxacin) prohibited from use in food-producing species by the FDA should ever be administered to any animal that has the potential to enter the human food chain. This includes rabbits, deer, and other free-ranging animals that are rehabilitated and released back into their native habitats and could subsequently be harvested by hunters for human consumption. If residues of an FDA-prohibited drug are detected in any edible animal-derived product, the prescribing veterinarian can be held legally responsible. Furthermore, FARAD never provides a WDI for any FDA-prohibited drug and recommends that any animal treated with an FDA-prohibited drug never enter the human food chain.

Wildlife Species for Which Drug WDI Recommendations Are Commonly Requested

Over the last 20 years, FARAD has received numerous requests for WDIs following ELDU in wildlife. The 10 most common drugs for which FARAD received WDI requests following ELDU in wildlife species between 1998 and 2018 were summarized **(Table 3)**.

Game birds and waterfowl

Currently, there are 19 drugs approved by the FDA for use in game birds (Table 1). Nevertheless,

Table 3—Summary of drugs for which FARAD most frequently received WDI requests for wildlife species from January 1, 1998, to January 1, 2018.

Drug	No. of WDI requests
Meloxicam	85
Enrofloxacin*	57
Tiletamine hydrochloride–zolazepam hydrochloride	57
Amoxicillin	50
Xylazine hydrochloride	50
Sulfadimethoxine	47
Fenbendazole	44
Ivermectin	44
Oxytetracycline	38
Penicillins	32
All other drugs	654

The top 10 drugs for which FARAD received WDI requests for wildlife species are listed individually. Wildlife species included bison, buffalo, cervids (deer and elk), water fowl (ducks, geese, swans), game birds (quail, pheasant, peacock, and partridge), rabbits, wild boars, sea lions, bears, opossum, pigeons, doves, turtles, fish, and shellfish. *Extralabel use of fluoroquinolones in food-producing species is prohibited by the FDA, and FARAD is not allowed to give WDI recommendations in those cases.

FARAD often receives WDI requests following ELDU of meloxicam, sulfadimethoxine, fenbendazole, ivermectin, and amprolium in game birds.

For game birds (particularly ducks and geese), meloxicam is the most common drug for which WDI requests are submitted to FARAD. Meloxicam is a cyclooxygenase-2 preferential NSAID approved by the FDA for use in dogs and cats. There are no FDA-approved meloxicam formulations for use in food-producing animals in the United States; therefore, detection of meloxicam residues in any edible animal tissue is a violation (ie, the regulatory tolerance is 0). The respective drug regulatory agencies of Australia, Canada, and New Zealand have approved use of injectable formulations of meloxicam in cattle, sheep, and swine. Unfortunately, FARAD has not been able to find any published tissue residue data for meloxicam in wildlife species. However, there are limited published data regarding the plasma pharmacokinetics of meloxicam in buffalo (*Bubalus bubalis*),[61-63] yak,[64] ostriches (*Struthio camelus*),[65] chickens, turkeys, and pigeons.[66,67,e] Estimation of a WDI from plasma pharmacokinetic data is not optimal because that data may not reflect the tissue pharmacokinetics of drugs.

Sulfadimethoxine is approved by the FDA for use in ducks, chickens, turkeys, and partridges, and the sulfadimethoxine tolerance is 100 ppb in edible tissues derived from those species. However, when sulfadimethoxine is administered in an extralabel manner to other avian species, the detection of any residues of the drug in edible tissues derived from treated animals is considered a violation (ie, the tolerance is 0), and an extended WDI is required to be in compliance with AMDUCA. Because pharmacokinetic data for sulfadimethoxine are not currently available for any game bird species, FARAD likewise recommends a prolonged WDI.

Another drug for which FARAD frequently receives WDI requests for game birds is the anthelmintic fenbendazole. Fenbendazole is not approved by the FDA for use in game birds, and although there are limited plasma pharmacokinetic data available for the drug in game birds,[68-72] tissue depletion data in those species are currently lacking. In 1 study[70] in which pheasants were administered various doses of fenbendazole in the feed for 21 consecutive days and then euthanized (no WDI), tissue concentrations of the drug and its metabolites were very low. However, because fenbendazole is not approved by the FDA for use in pheasants or any other game bird species, the detection of any residue of the drug in edible tissues from those species is considered a violation.

Extralabel use of ivermectin in waterfowl also generates frequent requests to FARAD for WDI recommendations. Unfortunately, tissue residue data for ivermectin in waterfowl are currently lacking.

Amprolium is approved by the FDA for use in pheasants as a feed additive for the prevention of coccidiosis. The liver tolerance for amprolium in pheasants is 1 ppm.[12] Limited tissue amprolium data are available for pheasants[73] but no other game bird species.

Cervids

Fourteen drugs are currently approved by the FDA for use in cervids. However, FARAD frequently receives requests for WDIs for ivermectin, oxytetracycline, tiletamine-zolazepam, xylazine, and other drugs commonly used for immobilization in cervids. Requests for WDIs for the sedative antagonists yohimbine, naltrexone hydrochloride, and atipamezole are also common.

Ivermectin is approved by the FDA for use in reindeer but not other cervid species for the treatment and control of warbles (*Oedemagena tarandi*).[12] The meat WDT for reindeer following administration of ivermectin in accordance with the FDA-approved label is 56 days, and the liver tolerance for the drug is 15 ppb.[12] Limited tissue residue data following SC and PO administration of ivermectin are available for reindeer[74-77] but not other cervid species.

Oxytetracycline is an antimicrobial approved by the FDA for use in many food-producing species, such as cattle, swine, sheep, chickens, turkeys, finfish, and lobster, but is not approved for use in any cervid species. Plasma, muscle, and liver residue data following administration of oxytetracycline to cervid species are available but sparse.[78-80]

Plasma and tissue residue data for anesthetics and antagonist drugs in cervids are also limited.[81] Xylazine is approved by the FDA for use in elk and deer for sedation or as an analgesic or preanesthetic agent; however, the label specifically states that the drug is approved for use in elk and deer not intended for human consumption. Therefore, tissue tolerances for xylazine have not been established for cervids, and the detection of any xylazine residue in edible tissues of cervids is a violation. Yohimbine, a pharmacological antagonist selective for α_2-adrenergic receptors, is approved by the FDA for use in captive and free-ranging deer

and elk as a reversal agent for xylazine. Although the FDA-approved label states that yohimbine should not be used in domestic food-producing animals and tissue tolerances for yohimbine have not been established for any species, the label also states that the drug should not be administered to deer and elk for 30 days before or during hunting season, which is suggestive of a meat WDT. Pharmacokinetic data for yohimbine are lacking for cervids, but there are some limited pharmacokinetic data for yohimbine in cattle.[82]

The pharmacological antagonist naltrexone is approved by the FDA for use in elk and moose as an antagonist for carfentanil citrate (a synthetic opioid that has been voluntarily withdrawn from the market by the manufacturer). This is another drug for which the label specifically states it is not for use in domestic food-producing animals and specifies that it should not be administered to elk and moose for 45 days before or during hunting seasons.[12] Tissue tolerances for naltrexone have not been established for any species.[12] Pharmacokinetic data for naltrexone in elk and moose are lacking, but the pharmacokinetics of naltrexone have been investigated in common eland (*Taurotragus oryx*), another cervid species.[83] Results of that study[83] indicate that the plasma half-life of naltrexone is fairly short (3.7 hours) when it is administered after carfentanil. It is believed that naltrexone has a longer half-life than other opioid antagonists, which makes it a safer alternative for reversing potent opioids, such as carfentanil, because it decreases the risk for renarcotization.[84-87] However, the long half-life of naltrexone suggests that a prolonged WDI may be necessary to avoid violative tissue residues of the drug.

Only limited data are currently available regarding the depletion of atipamezole in wildlife.[43,81,88] In a study[43] involving reindeer, the plasma elimination half-life for atipamezole (59.9 minutes) was shorter than that for medetomidine (76.1 minutes), which resulted in the animals becoming resedated 30 to 60 minutes after atipamezole administration.

Bison and buffalo

Five drugs are currently approved by the FDA for use in bison, but there are limited tissue residue data available for most drugs in bison and buffalo. It is important to note that, although bison (*Bison bison*), buffalo (*Bubalus bubalis*), and domestic cattle (*Bos taurus*) all belong to the Bovidae family, they are 3 distinct species, and many drugs are metabolized and eliminated differently among species.

Florfenicol is the most common drug for which FARAD receives WDI requests for bison and buffalo. Other drugs for which FARAD commonly receives WDI requests for bison and buffalo include avermectins (doramectin and eprinomectin), xylazine, tulathromycin, flunixin, and sulfadimethoxine. There are currently no pharmacokinetic data for florfenicol in bison, but there are a substantial amount of plasma, milk, and tissue data available following the use of florfenicol in domestic cattle. Only limited plasma and milk, but no tissue, pharmacokinetic data are available for avermectins in buffalo.[89,90,f] Plasma and milk pharmacokinetic data were determined following SC administration of doramectin to buffalo.[f] The plasma and milk pharmacokinetics of eprinomectin and moxidectin have been reported following topical application of those drugs to lactating water buffalo.[90] Results of that study[90] indicate that the systemic availability of moxidectin following topical administration in water buffalo is similar to that for domestic cattle; however, the concentration of moxidectin achieved in the milk of water buffalo was substantially higher than that in domestic cattle, which suggests that an extended WDI is required for moxidectin when it is administered to water buffalo. In contrast, the systemic availability of eprinomectin following topical administration to water buffalo was lower than that reported for domestic cattle but similar to that reported for sheep.[90] For the water buffaloes of that study,[90] the milk concentration of eprinomectin was lower than the milk concentration of moxidectin, which suggests that the WDI for eprinomectin following topical application was shorter than that for moxidectin in water buffalo. Pharmacokinetic data for xylazine are available for cattle[51,91,92] but not buffalo. Serum pharmacokinetic data for tulathromycin following SC administration to bison are limited,[93,94] but serum or plasma and tissue pharmacokinetic data are available for tulathromycin following administration to cattle,[95-100,g] goats,[101-107] and sheep.[108,109] Although extensive plasma and tissue pharmacokinetic data are available for flunixin in cattle, goats, and sheep, we are aware of only 1 study[110] in which the plasma pharmacokinetics of flunixin were determined for buffalo. Sulfadimethoxine is approved by the FDA for use in cattle, and the established tolerance for sulfadimethoxine in edible tissues is 100 ppb. Requests for WDIs for sulfadimethoxine in both milk and meat products of bison have been received by FARAD. The pharmacokinetics of sulfadimethoxine in plasma and milk of buffalo have been described in 4 studies.[111-114]

For many drugs administered to bison and buffalo, tissue pharmacokinetic data are available for cattle, goats, and sheep. Extrapolation of that data to other ruminant species is possible, but that extrapolation should be done with caution and WDIs should be appropriately extended.

Rabbits

Sulfaquinoxaline and lasalocid sodium are the only 2 products currently approved by the FDA for use in rabbits. Thus, FARAD often receives requests for WDIs following ELDU in rabbits.

The most common drug for which FARAD receives WDI requests for rabbits is sulfadimethoxine. Administration of sulfadimethoxine to rabbits has been evaluated in multiple studies,[115-125] but the de-

pletion of the drug from the tissues of rabbits was described in only 1 study.[126] The most frequent reason provided to FARAD for ELDU of sulfadimethoxine in rabbits is the treatment of coccidiosis. For rabbits, sulfaquinoxaline is labeled for the prevention and control of coccidia and lasalocid sodium is labeled for the prevention of coccidia; therefore, FARAD recommends that 1 of those 2 FDA-approved drugs be used to treat coccidiosis in rabbits to be in compliance with AMDUCA.

Other drugs for which FARAD commonly receives WDI requests for rabbits include fenbendazole, ivermectin, amprolium, xylazine, and meloxicam. Currently, only 3 studies[69,71,127] provide plasma elimination data for fenbendazole following oral or IV administration to rabbits. There is 1 study[128] that describes tissue elimination data for ivermectin following SC administration to rabbits; results indicate that the drug is widely distributed and has the potential to exist in high concentrations in tissues for a prolonged period of time.

The number of requests for WDIs following ELDU of amprolium in rabbits has risen considerably over the last 2 years (25 WDI requests between 1996 and 2018 [1.14 requests/y], which included 13 WDI in 2017 and 2018 [6.5 requests/y]). Compliance policy guide 615.115[19] does not prohibit the administration of amprolium in the feed or water of rabbits. However, it is considered ELDU, and tissue tolerances for amprolium in rabbit tissues have not been established. Therefore, the detection of amprolium in any edible tissue derived from rabbits would be considered a violation. Pharmacokinetic data for amprolium are sparse for food-producing species in general and are completely lacking for rabbits.

Xylazine is commonly used as a sedative, analgesic, or preanesthetic agent in rabbits; however, there are currently no pharmacokinetic data for xylazine in any rodent or lagomorph species. Requests for WDIs following oral administration of meloxicam to rabbits are occasionally received by FARAD, and plasma elimination data for meloxicam following oral administration of single or multiple doses of the drug to rabbits are available.[129-131]

Rabbits and other lagomorph species are cecotrophic, which presents a challenge for the estimation of WDIs regardless of the drug administered. Unmetabolized parent drugs that are incorporated into cecotrophes (ie, night feces) and reingested by the treated animal (or a cohort animal with access to the feces from the treated animal) can contribute to the persistence of tissue drug residues for prolonged periods and increase the risk for violative residues.[132]

Summary

The purpose of this FARAD Digest is to provide US veterinarians guidance regarding ELDU in wildlife and game animals. Because few drugs have been approved by the FDA for use in nondomestic species, ELDU in wildlife and game animals is common. Regardless of the drug, tissue tolerances have typically not been established for species that are not included on the FDA-approved label. In the absence of an established tolerance for a particular drug in a species, the detection of that drug or any of its metabolites in edible tissues derived from treated animals of that species is considered a violation and subject to regulatory action (ie, the default tolerance is 0). Pharmacokinetic data are generally lacking or limited for nondomestic species. Therefore, to be conservative and minimize the risk for violative residues, FARAD typically recommends prolonged WDIs for drugs following ELDU in wildlife and game species. Given that the fate of wildlife species is unknown, it is best that animals with the potential to enter the human food chain be considered food-producing species and not be anesthetized or treated and released into their native habitats during hunting season. If wildlife or game animals must be administered drugs that might cause residues in edible tissues and are released into their native habitats before the recommended WDT or WDI has expired, it is recommended that those animals be identified in some manner to alert hunters who might subsequently harvest the animals that the meat should not be consumed before a particular date or consultation with appropriate responsible parties or authorities.

Veterinarians should be aware of the requirements outlined by AMDUCA for legal ELDU to safeguard the human food supply while continuing to promote the health and welfare of wildlife species. Given the ongoing generation of pharmacokinetic and tissue residue data, veterinarians are encouraged to contact FARAD for WDIs following ELDU in food-producing species, even for drugs for which FARAD has not previously been able to recommend a WDI, because new information may have become available in the intervening period. Additional information regarding drug residue avoidance and WDIs for food-producing species is available on the FARAD website.[133] Veterinarians are encouraged to abide by the veterinary oath, professional standards, and existing laws to the best of their abilities to avoid residue violations in human food products that are of animal origin.

Acknowledgments

Footnotes

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