

Considerations for extralabel drug use in calves

Danielle A. Mzyk BS

Ronette Gehring BVSc, MMedVet

Lisa A. Tell DVM

Thomas W. Vickroy PhD

Jim E. Riviere DVM, PhD

Gail Ragan BA

Ronald E. Baynes DVM, PhD

Geof W. Smith DVM, PhD

From the Food Animal Residue Avoidance and Depletion Program (FARAD), Department of Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606 (Mzyk, Baynes, Smith); FARAD, Institute of Computational Comparative Medicine, Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506 (Gehring, Riviere, Ragan); FARAD, Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA 95616 (Tell); and FARAD, Department of Physiological Sciences, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610 (Vickroy).

Address correspondence to Ms. Mzyk (dalindqu@ncsu.edu).

Calfhood diseases have major negative economic consequences on beef and dairy operations owing to costs associated with treatment, long-term effects on growth and performance, and death of affected calves.¹⁻³ The number of drugs approved for the treatment of diseased calves by the FDA is limited; however, veterinarians have the authority to administer drugs in an extralabel manner to that class of animals under provisions established by AMDUCA.⁴ Nevertheless, drug labels that state, “a withdrawal period has not been established for this product in preruminating calves” can cause confusion about whether those drugs can or cannot be administered to young calves. Pharmacokinetic and residue depletion studies for very few drugs have been performed in young calves, and extrapolation of drug WDTs established for adult cattle to calves might not be appropriate or adequate to avoid violative tissue residues, which makes ELDU in calves problematic and potentially difficult to justify. The purpose of this digest is to provide veterinarians with a summary of the considerations for ELDU in both beef and dairy calves as well as calves intended for veal production.

Classification of Calves

From a regulatory standpoint, an important issue in regard to appropriate and legal drug use is interpretation of the terms preruminant and ruminant cattle. This issue is muddled by the fact that FDA definitions for target animal (or production) classes occasionally overlap or are inconsistent. For example, the FDA defines preruminant as “immature cattle (including dairy breeds) lacking a

functional rumen and intended for meat production,”⁵ which is the same definition used for veal calves.⁶ Physiologically, all calves, regardless of their breed or intended use, begin life as preruminants. However, the FDA distinguishes veal calves from other classes (suckling and dairy) of calves because of their handling, housing, and proximity to slaughter.⁶ Dairy calves are defined as immature cattle of dairy breeds from birth until weaning that are fed a ration, which includes milk or liquid milk replacer.⁶ Suckling calves are defined as immature cattle (generally of beef breeds) from birth until weaning that are maintained with and dependent on their dams for nourishment.⁶ The diet, management, and husbandry of calves within each of those classes differ and affect the development and maturation of hepatic and renal functions. Unfortunately, little research has been done to compare differences in the pharmacokinetic profiles of drugs following administration to calves of various ages among those 3 classifications.

Because of the confusion associated with interpretation of the term preruminant, in this digest, the term calves will be used to refer to preruminant cattle in general discussions, and dairy heifer, beef steer, and veal calves will be used as appropriate for specific discussions. For the purpose of this digest, dairy heifers are defined as female dairy calves that are intended to be raised for milk production. Beef steers are male calves of both dairy and beef breeds that are intended for meat production and are slaughtered when they are > 9 months old. Veal calves are calves that are intended for veal production and are slaughtered at various ages up to 18 weeks (4.5 months) old.

Effect of Maturation on Drug Metabolism

Rumen development is a dynamic process that occurs over a period of time; therefore, determining the exact moment that a young calf transitions from a preruminant to ruminant animal is difficult.

ABBREVIATIONS

ELDU	Extralabel drug use
FARAD	Food Animal Residue Avoidance and Depletion Program
FSIS	Food Safety and Inspection Service
VFD	Veterinary Feed Directive
WDI	Withdrawal interval
WDT	Withdrawal time

The rates of rumen development and maturation vary among calves and are dependent on nutrition and diet.⁷ At birth, the rumen is small, and the development and maturation of rumen function are delayed in calves fed milk diets exclusively relative to calves that are not fed milk diets exclusively. When calves are fed starter, or grain, the microbial population in the rumen begins to ferment carbohydrates into volatile fatty acids (butyric, propionic, and acetic acids). The production of butyric acid, and to a lesser extent propionic acid, is primarily responsible for rumen maturation and the development of functional rumen papillae.⁸ In cattle, rumen function has a substantial effect on the pharmacokinetics of drugs, and changes in the rumen pH, extracellular fluid composition, and motility and transit time of the gastrointestinal tract as calves mature affect the solubility and absorption of orally administered drugs. Also, rumen microflora can inactivate orally administered drugs, thereby decreasing drug bioavailability and absorption.⁹

Although rumen development affects drug absorption, it is maturation of the elimination pathways of the liver and kidneys, the primary organs responsible for drug clearance, that greatly affects drug metabolism and excretion, which in turn affect tissue drug residues. In fact, there is considerable ongoing research in both human and veterinary medicine on the effects of organ development on drug metabolism and elimination. Results of multiple pharmacokinetic studies¹⁰⁻¹⁶ indicate that the plasma elimination half-life, clearance rate, and volume of distribution for many drugs vary substantially between calves and adult cattle. Veterinarians should also be cognizant that plasma pharmacokinetic parameters do not necessarily accurately reflect drug dynamics in organs and tissues.¹⁷

Research regarding the ontogeny of transport systems involved in the uptake or biliary and renal excretion of drugs in cattle is limited. Hepatic metabolism, which usually involves a 2-step elimination process (phases I and II), is the main mechanism of drug elimination.^{18,19} Phase I metabolism typically involves reactions mediated by cytochrome P450 enzymes, which increase the hydrophilicity of many compounds. In calves, cytochrome P450 enzyme activity increases 2-fold during the first week after birth and remains constant thereafter.²⁰ Mixed-function oxidase activity also develops over time, with some enzyme activities in 1-day-old calves only 17% to 50% of those in 42-day-old calves.²⁰ Phase II reactions contribute primarily to the systemic clearance of drugs by a series of conjugation pathways and other enzymes. Xenobiotic-metabolizing enzymes are generally deficient in food-producing animals at birth and gradually increase during the first few months after birth.²¹ Protein and enzyme expression for many cytochrome P450 enzymes are generally low at birth, and the birth process initiates their postnatal development.²² That mechanism likely contributes to the decrease in the elimination half-life and increase in the clearance rate observed for many drugs as calves

mature.

The maturation of renal pathways is dependent on renal blood flow and glomerular filtration rate. At birth, there is a large decrease in renal vascular resistance and increase in cardiac output and renal blood flow, which contribute to the growth and maturation of renal tubules and tubular processes.²³ For drugs that are dependent primarily on renal excretion, immature renal clearance mechanisms can result in a prolonged elimination half-life, but the pharmacokinetic parameters for those drugs are quite variable and complex owing to factors other than renal clearance such as protein binding and affinity.²⁴

Differences in pharmacokinetic parameters between calves and adult cattle can also be attributed to alterations in total body water content and rapid changes in plasma protein concentrations that occur as ruminants mature.^{25,26} The volume of distribution for a drug represents the proportion of drug measured in a specific biologic fluid relative to the total amount of drug in the body.²⁷ Thus, as the volume of distribution for a drug increases so does the likelihood that the drug will be detectable in body tissues, whereas as the volume of distribution for a drug decreases, it becomes more likely that the drug is confined to the central compartment (circulatory system).¹⁷ Compared with adult cattle, calves generally have greater total body water and extracellular fluid contents and lower adipose tissue and muscle mass. Changes in total body water and fat content as calves mature likely play a role in the age-dependent differences in distribution observed for many drugs.²⁴ For many drugs, the tissue elimination half-life is substantially longer for young calves than for adult cattle. Given that many drugs commonly administered to calves are approved for use in adult cattle, the WDTs for those drugs, which are based on several factors such as the established tolerance and drug pharmacokinetics in target tissues of healthy adult cattle, may not be adequate to avoid violative tissue residues when those drugs are administered to young calves.

Legal Considerations for the Treatment of Calves

In the United States, AMDUCA allows licensed veterinarians acting within a valid veterinarian-client-patient relationship to use and prescribe FDA-approved animal drugs in a manner that deviates from the approved label or FDA-approved human drugs for the treatment of disease in animals of various species, including food-producing species such as calves,²⁸ as long as that use is in accordance with the FDA regulations established in the US Code of Federal Regulations Title 21 part 530.⁴ Those regulations limit ELDU for the treatment of an animal when the health of that animal is threatened or suffering or death may result from failure to administer a drug in an extralabel manner. Veterinarians who use or prescribe drugs in an extralabel manner in food-producing animals

are required to set an extended withdrawal period for the marketing of meat or milk from those animals on the basis of scientific information and take other steps to prevent violative drug residues.

Veterinarians should be aware that the detection of tissue residues of any drug that does not have an established tolerance for that tissue is considered a violation, regardless of the age of the animal. The tolerance is established by the FDA and is defined as the maximum concentration of a veterinary drug residue (the residue may be the parent drug, metabolite, or some other marker residue that has been accepted for monitoring purposes) that is legally permitted or recognized as safe in specific edible tissues of treated animals.²⁹ Also, sensitive multidrug residue analytic methods continue to be developed that can detect drug residues at low concentrations that were previously undetectable, and the FSIS is implementing those methods in its routine surveillance protocols.³⁰ Thus, given that few drugs are approved for use and have established tolerances in calves, extralabel administration of most drugs to calves will require adherence to extended WDIs to minimize the risk of violative tissue residues.

Before proceeding, readers are reminded that there is an important distinction between WDT and WDI. The WDT is defined as the time required after administration of a drug in accordance with the label for tissue concentrations of the drug or its metabolites to decrease below established tolerances, whereas the WDI is a scientifically derived recommended withholding period for meat or milk products from animals following administration of a drug in an extralabel manner.³¹

FDA-Approved Drugs for Calves

In general, administration of a drug approved by the FDA for use in calves in accordance with the labeled dosage and adherence to the labeled WDT should be sufficient to avoid the detection of violative tissue residues. However, in the United States as of January 2016, only 18 drugs were approved by the FDA for use in all classes of calves, and many of those drugs no longer appear in the *Compendium of Veterinary Products*³² and may not be commercially available.

For many FDA-approved veterinary drugs, it can be difficult to discern from the label whether a specific drug is approved for use in young calves owing to variability in the type of data provided to the FDA by the drug sponsor. Because veal calves are slaughtered at a much younger age and differ physiologically from other classes of calves and there is limited tissue depletion information for that class of calves, drugs with labels that contain the statement “not for use in calves to be processed for veal” should not be administered to veal calves, and if they are administered, greatly extended WDIs are warranted. That statement indicates that the product has not been evaluated in calves intended for veal production and there is limited tissue depletion data, so withdrawal

recommendations may not be possible. According to FARAD’s interpretation, when a drug label states, “a withdrawal period has not been established for this product in preruminating calves,” it indicates that the drug can be legally administered to dairy heifer, beef steer, and veal calves provided all stipulations of AMDUCA are met, there is sufficient scientific data available to determine an appropriate WDI, and the drug in question is not prohibited from use in food-producing animals by the FDA.

For drugs approved for use in food-producing animals, residue tolerances are established for only the species and animal production classes for which that drug is approved. When a drug is administered to an unapproved species or production class (ie, ELDU), detection of any tissue residue of that drug is considered a violation. Target tissue data specific for calves are generally lacking for most drugs approved for use in adult cattle; therefore, residue depletion studies are warranted to characterize and extrapolate adult cattle data to young calves for calculation of appropriate WDIs. Drug label information and established tolerance concentrations for residues in meat and milk intended for human consumption are available on the FDA Animal Drugs³³ and FARAD VetGram³⁴ websites.

Medicated Feeds and Feed Additives

According to title 21, part 558 of the US Code of Federal Regulations,³⁵ a medicated feed is defined as any manufactured or mixed feed that contains drug ingredients intended to promote growth or feed efficiency or to cure, mitigate, prevent, or treat diseases of nonhuman animals. Several medicated feed additives are approved for use in various classes of calves, and complete information regarding those additives is available on the FARAD VetGram website.³⁴ In the United States, medicated feeds or feed additives cannot be administered in an extralabel manner to major species such as cattle, but can be administered in an extralabel manner for treatment purposes to minor species, such as goats and sheep. In other words, in major species (cattle, pigs, horses, dogs, cats, turkeys, and chickens), medicated feeds or feed additives cannot be used or prescribed for an unapproved species or production class or at a higher or lower dose than that provided on the FDA-approved label.

Medicated milk replacers

In the United States, the FDA considers milk and milk replacer fed to calves as feeds; therefore, they are subject to the same rules and regulations as other feeds. A large proportion of the antimicrobials administered to dairy calves are fed via milk replacer.³⁵ Neomycin and oxytetracycline are approved for use in milk replacers for the prevention or treatment of bacterial enteritis (scours). Historically, those medications could be continuously fed throughout the preweaning period. Results of a 2014 national survey³⁵ indicate that approximately 60% of US dairy operations feed medicated milk replacers to preweaned

calves, and most of those milk replacers contain a combination of oxytetracycline and neomycin. However, there is little data available to indicate that administration of antimicrobials to calves via milk or milk replacer is effective for the prevention of scours, and that practice should be discouraged.³⁶

In 2010, the FDA mandated that milk replacers could no longer contain neomycin and oxytetracycline in a ratio of 2:1.³⁷ Instead, milk replacers can contain neomycin and oxytetracycline in a ratio of 1:1 and can be fed at either a low (0.11 to 0.22 mg/kg [0.05 to 0.10 mg/lb]) or high (22 mg/kg [10 mg/kg]) dose for only 7 to 14 days.³⁷ Thus, calves can no longer be fed milk or milk replacers containing antimicrobials continuously from birth to weaning. This was an effort to transition the use of oral antimicrobials in calves from prophylactic to therapeutic purposes. Nevertheless, 296 residue violations were detected in veal calves in 2014, of which 152 (51%) were caused by neomycin and oxytetracycline.³⁸

Waste milk and colostrum

On US dairy operations, it is common practice to feed calves unsaleable or waste milk from cows that may potentially contain drug residues.³⁵ That practice has been associated with violative tissue drug residues in calves,³⁹ and FARAD has estimated slaughter WDIs for veal calves fed colostrum from cows treated with antimicrobials during the dry period (ie, the approx 45- to 60-day period prior to calving during which a dairy cow is not milked).⁴⁰ Results of other studies^{41,42} likewise indicate that feeding calves milk replacer containing penicillin G or amoxicillin can result in violative tissue residues of those drugs. In 1988, calves fed milk or colostrum from medicated cows accounted for 39 of the 460 (8.5%) residue violations identified by the FDA.⁴³ In contrast, residues of cephalirin benzathine were not identified in the tissues of 24- or 48-hour-old calves that were fed first-milking colostrum from cows that were administered that drug by an intramammary route in accordance with the product label at dry off (ie, the first day of the dry period).⁴⁴ Although the results of that study⁴⁴ cannot be used to indicate that feeding calves colostrum from medicated cows will never cause violative tissue residues, it appears the risk is fairly low, especially when cows are treated with drugs in accordance with the FDA-approved label. Data regarding violative tissue residues in calves fed milk or colostrum from cows treated with drugs in an extralabel manner are lacking.

The adulteration of a medicated feed consisting of cows' milk mixed with a drug that has not been directed by an approved label to be fed to veal calves would be considered extralabel use of a medicated feed and considered unsafe by the FDA.⁴⁵ Previous regulatory action has been documented when drugs have been administered in contaminated milk to veal calves.⁴⁶ Producers and veterinarians are liable for the presence of any violative residues in animals that enter the human food chain; therefore, calves fed milk that potentially contains a drug residue should not be used for veal production.

VFD

The FDA recently enacted (January 2017) the VFD,⁴⁷ which outlines the regulations for the administration of drugs in animal feeds. The VFD limits the use of medically important antimicrobials (ie, antimicrobials considered necessary for ensuring human and animal health) in animal feeds for therapeutic purposes only; those antimicrobials cannot be administered to facilitate growth or feed efficiency.⁴⁷ It also requires veterinary oversight (ie, prescription) for all antimicrobials administered in animal feeds and prohibits ELDU of any antimicrobial or other drug in feed intended for food-producing animals.⁴⁷ The VFD regulations apply to medicated milk replacers and any other drugs that might be added to milk fed to calves.⁴⁷ Thus, calf raisers must follow the label directions when feeding a medicated milk replacer. Moreover, because the FDA considers milk and milk replacer animal feeds, veterinarians cannot prescribe the administration of any drug in milk or milk replacer in an extralabel manner. However, oral administration of drugs separate from feed (including milk and milk replacer) is permissible as long as such administration is in accordance with the FDA-approved drug label or AMDUCA.⁴⁷

State Regulations Regarding Drug Administration to Calves

Results of an extensive search and review of laws regarding drug and antimicrobial use in food-producing animals conducted by FARAD personnel revealed that 8 states (California, Maryland, Minnesota, New Jersey, New York, North Carolina, Pennsylvania, and West Virginia) have introduced at least 1 bill to the respective state legislatures that would affect drug use in food-producing animals. As of August 2016, the only bill introduced at the state level that was signed into law was California Senate Bill 27.

California Senate Bill 27 is intended to promote the judicious use of medically important antimicrobials in food-producing animals and is similar to the VFD in many ways.⁴⁸ It restricts the use of antimicrobials deemed important for human medicine in livestock to therapeutic purposes only and requires that such use be in accordance with a prescription written by a licensed veterinarian within the confines of a valid veterinary-client-patient relationship. However, California Senate Bill 27 applies to all antimicrobials regardless of route of administration, whereas the VFD applies only to antimicrobials administered in water or feed. Consequently, in California, injectable antimicrobials currently available over-the-counter will be available by prescription only beginning on January 1, 2018.⁴⁸

Drugs Commonly Prescribed to Calves

A few select drugs commonly administered to calves for which FARAD frequently receives queries

were summarized (**Table 1**). As a reminder, tissue tolerances are established only for drugs that are administered to an approved species according to the label instructions, and the detection of tissue residues that exceed the tolerance for a particular drug or for a drug for which a tolerance has not been established is a violation. Because drug metabolism can vary on the basis of age or health status, multiple tests have been developed to detect various drugs in urine or other fluid or tissue matrices, and those tests can be used to evaluate samples obtained from calves prior to slaughter as an additional means of ensuring that those calves do not have violative tissue residues. However, when considering the use of such a test, it is critical that the test chosen can detect the compound of interest at or below the tolerance established for the tissue being assessed. For example, a commercially available cow-side test^a can detect certain sulfonamides in the urine and serum of cattle, but its limit of detection is greater than the established tolerance for sulfonamides in tissues; therefore, it should be used with caution, and a negative test result should not be considered a guarantee that violative tissue residues are not present.

Sulfamethoxazole and trimethoprim

Sulfonamides are of high regulatory concern for the FDA and have the potential to accumulate in tissues with repeated dosing. A tolerance for sulfonamides has not been established for calves; therefore, detection of any sulfonamide residue in the tissues of a calf is considered a violation. In calves, the elimination rate of sulfamethoxazole in tissues is 10-fold slower than that in plasma, and the elimination half-life of sulfamethoxazole following IM injection was 70.6 and 81.6 hours for muscle and kidney, respectively.⁴⁹ Excretion of sulfonamides can be erratic, especially in young animals; therefore, assessment of urine for sulfonamide residues is advisable for any compromised animal, and the WDI for calves should be greatly extended, compared with that for adult cattle.

Tetracyclines

Tetracyclines are commonly administered to calves in medicated milk replacers. In the United States, tetra-

acyclines can be administered to calves as long as the guidelines established by the VFD⁴⁷ and AMDUCA⁴ are followed. In young calves, the terminal half-life of oxytetracycline following oral administration in milk or milk replacer is longer than that following parenteral administration,^{50,51} likely because tetracycline binds to calcium in the milk or milk replacer, which extends its absorption phase. Following IV administration of oxytetracycline, the mean clearance and volume of distribution in 3-week-old calves are 2- and 3-fold, respectively, greater than the corresponding values for adult cows.⁵² Several products containing oxytetracycline are approved by the FDA for use in calves, and the WDTs range from 18 to 28 days when those products are administered in accordance with the approved label. According to the label of several oxytetracycline products, it is recommended that the volume of tetracycline parenterally administered at each injection site be limited to 1 to 2 mL in small calves that weigh < 45 kg (100 lb) because injection of larger volumes at each injection site may necessitate a prolonged WDT.

Flunixin meglumine

Flunixin meglumine is an NSAID that, in the United States, is approved for the treatment of pyrexia associated with bovine respiratory disease, endotoxemia, and acute mastitis and inflammation caused by endotoxemia in beef and dairy cattle. It also has analgesic properties and is frequently used in an extralabel manner to alleviate signs of pain associated with castration and dehorning in calves.⁵³⁻⁵⁵ From October 2013 through September 2014, the FSIS identified residue violations in 1,146 animals processed in US slaughter houses, of which 108 (10%) were caused by flunixin; 17 of the 108 (16%) animals with violative flunixin residues were immature cattle (veal calves [n = 9] and heavy calves [ruminating animals typically slaughtered at > 182 kg {400 lb}; 8]).³⁸ In 1 study,¹¹ veal calves administered flunixin (2.2 mg/kg [1 mg/lb], IV, q 24 h for 3 days [ie, the labeled dosage for adult cattle]) had detectable concentrations of that drug in both liver and muscle tissue for at least 5 days after injection of the last dose. Flunixin is a drug of high regulatory concern for the FDA. Because

Table 1—Tissue elimination half-lives in calves and adult cattle for select drugs commonly administered to calves.

Drug	Calves		Adult cattle		Current FSIS analytic lower limit of detection (µg/mL)	FDA-established tolerance ⁷⁰	
	Tissue	Elimination half-life (h)	Tissue	Elimination half-life (h)		Tissue	Tolerance (µg/mL)
Sulfamethoxazole-trimethoprim*	Muscle	70.6 (49)	Muscle	65.3 (73)	0.05 (77)	All edible tissues (including kidney†)	0.1
Oxytetracycline	Kidney	81.1 (50)	Kidney	21.7 (74)	0.5 (78)	Kidney	12
	Muscle	55.9 (50)	Muscle	11.6 (74)		Muscle	2
Flunixin	Liver	137.25 (11)	Liver	27.94 (15)	0.0125 (79)	Liver	6
	Kidney	152.74 (11)	Kidney	21.53 (15)		Liver†	0.125
Florfenicol	Kidney	10.34 (75)	Liver	206 (76)	0.2 (80)	Muscle	0.025
						Liver†	3.7
						Muscle	0.3

Numbers in parentheses represent the numbers of the references from which the information was obtained. Of the drugs listed, only oxytetracycline is approved for use in calves; administration of the other drugs to calves would be considered ELDU.

*In the United States, ELDU of all sulfonamides and potentiated sulfonamides is prohibited in female dairy cattle > 20 months old. †Target tissue (edible tissue selected by the FDA to monitor for residues in target animals).

the clearance and tissue elimination half-life of flunixin are dependent on the age and disease status of the treated animal, FARAD recommends a meat WDI of at least 14 days when flunixin is administered in accordance with the labeled dosage to dairy heifer, beef steer, and veal calves.¹¹ Further information regarding the avoidance of flunixin residues in cattle is available in a previous FARAD Digest.⁵⁶

Meloxicam

Meloxicam is an NSAID that is commonly administered to calves to alleviate signs of pain and inflammation associated with routine procedures such as dehorning and castration. Meloxicam is not approved for use in cattle in the United States; therefore, the detection of any meloxicam residue in the tissues or milk of cattle sold for human consumption is considered a violation, and extended WDIs are necessary to ensure that meloxicam residue concentrations are undetectable by the FSIS. In the United States, meloxicam is not prohibited from use in food animals; thus, all AMDUCA guidelines must be followed for permissible ELDU. The analgesic properties of meloxicam are greater than those of flunixin⁵⁷; therefore, since there are currently no drugs approved for alleviation of pain in cattle, the use of meloxicam for analgesic purposes appears to be permissible under AMDUCA.^{58,59}

Results of 1 study⁶⁰ indicate that 4- to 6-month-old beef steers administered meloxicam (0.5 mg/kg [0.23 mg/lb], PO, q 24 h for 4 days) had kidney and liver concentrations of the drug below the limit of quantitation (0.025 mg/kg [0.011 mg/lb]) by 15 days after administration of the last dose. Meloxicam is approved for use in cattle in other countries such as Canada and many countries in the European Union. In the European Union, meloxicam is approved for use in calves > 1 week old for the treatment of diarrhea in combination with oral fluid therapy to reduce clinical signs of the disease and in calves 6 to 12 weeks old to provide analgesia following dehorning; the approved dose is 0.5 mg/kg, PO, once, and the withdrawal period for slaughter is 15 days.⁶¹ In the United States, FARAD recommends a meat WDI of 21 days following oral administration of a single dose (0.5 to 1.0 mg/kg [0.23 to 0.45 mg/lb]) of meloxicam to calves and 30 days when multiple doses of up to 1 mg/kg of the drug are administered.

Cephalosporins

In April 2012, the FDA prohibited the ELDU of cephalosporins (excluding cephalixin) in major food-producing animals (cattle, swine, chickens, and turkeys) with some exceptions.⁶² Those exceptions permit the administration of a cephalosporin for an extralabel indication (ie, a disease or purpose not included on the approved label) as long as it is administered in accordance with the labeled dosage (dose, route, frequency, and duration of administration) approved for the species and production class.⁶³ Although the FDA currently considers veal calves as a separate production class from dairy heifer and beef

steer calves during the drug approval process,⁶ cattle of all ages and production classes are considered a major-use species and are subject to the ELDU prohibitions for cephalosporins.

Results of multiple pharmacokinetic studies^{10,64,65} indicate that, for any given cephalosporin, the plasma elimination half-life in calves is longer than that for adult cattle, and the plasma elimination half-life varies considerably by age and among cephalosporin formulations. For example, the plasma elimination half-life of ceftiofur sodium for calves ≤ 3 months old is almost 3 times that for calves 6 to 9 months old.¹⁰ Currently, FARAD recommends a conservative meat WDI of 14 days for dairy heifer and beef steer calves following administration of ceftiofur sodium at the labeled dosage (1.1 to 2.2 mg/kg [0.5 to 1.0 mg/lb], IM or SC, q 24 h for 3 days). The labels of several ceftiofur products specifically state that the drug cannot be used in calves intended for veal production, and those products should never be administered to veal calves. More tissue data are needed to determine WDIs for calves following the administration other formulations of ceftiofur.

Florfenicol

Florfenicol is a synthetic broad-spectrum antimicrobial that is approved for the control and treatment of bovine respiratory disease associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somnus* and treatment of bovine interdigital phlegmon (foot rot) in ruminant cattle (beef cattle and female dairy cattle < 20 months old).⁶⁶ The meat WDT is 28 days when it is administered IM and 38 days when it is administered SC.⁶⁶ An extended WDI should be observed when florfenicol is administered in an extralabel manner to calves. A meat WDI of 90 days is currently recommended by FARAD following administration of a single SC dose of florfenicol (40 mg/kg [18 mg/lb]) to dairy heifer and beef steer calves. Because florfenicol is not approved for use in veal calves, the detection of any florfenicol amine residue in the tissue of a veal calf at slaughter would be considered a violation. However, because florfenicol is approved for use in beef cattle, the detection of a florfenicol amine residue at a concentration lower than the established tolerance for that production class would not be considered a violation.

Fluoroquinolones

In 1997, the FDA prohibited the ELDU of all fluoroquinolones in food-producing animals.⁶⁷ Two fluoroquinolones, danofloxacin and enrofloxacin, are currently approved for use in cattle for the control and treatment bovine respiratory disease. The label for both of those products specifically states, “a withdrawal period has not been established for this product in preruminating calves.”^{68,69} Use in calves to be processed for veal would be an extralabel use, which is prohibited.⁶⁷ Therefore, a veterinarian cannot legally prescribe this drug for veal calves, no matter what withdrawal period is prescribed.

In regard to enrofloxacin, it is FARAD's interpretation that if a veterinarian documents in the medical record that a young calf is not intended for veal production (ie, dairy heifer or beef steer), use is permitted in female and male dairy breed animals (including suckling calves) that are raised for beef or dairy production, as long as all other conditions in the labeling are met. Thus, enrofloxacin could be administered in accordance with the approved label to such animals.

The label for danofloxacin⁶⁸ specifically states that the product is, "not for use in cattle intended for dairy production or calves to be processed for veal." Thus, danofloxacin cannot be legally administered to veal calves or dairy heifers intended for milk production, no matter what WDI is observed. According to FARAD's interpretation, administration of danofloxacin to female or male calves of dairy breeds that are intended for meat production would be legal provided it is documented that these calves are not being raised for veal and all other label instructions are followed because the FDA considers those animals beef cattle.

Summary

The purpose of this FARAD Digest was to provide US veterinarians guidance regarding drug administration to calves. The variable nomenclature used by the FDA and scientific literature to define calves and the various production classes thereof can cause confusion about the regulations that govern drug use in those animals. The lack of FDA-approved drugs for use in dairy heifer, beef steer, and veal calves frequently necessitates ELDU. Because tissue residue data for various drugs in young calves are limited, extended WDIs are generally necessary to avoid violative tissue residues. Beginning January 1, 2017, feeding medicated milk replacer and waste milk to calves will become more tightly regulated with the implementation of the VFD. Veterinarians need to be aware of those issues to safeguard the human food supply as well as to continue to promote the health and welfare of all calves.

Acknowledgments

Supported by a USDA grant for the Food Animal Residue Avoidance and Depletion Program.

Footnotes

- a. Kidney Inhibition Swab (KIS) test, Charm Sciences Inc, Lawrence, Mass.

References

1. Schaffer AP, Larson RL, Cernicchiaro N, et al. The association between calfhoo d bovine respiratory disease complex and subsequent departure from the herd, milk production, and reproduction in dairy cattle. *J Am Vet Med Assoc* 2016;248:1157-1164.
2. Virtala AM, Mechor GD, Gröhn YT, et al. The effect of calfhoo d diseases on growth of female dairy calves during the first 3 months of life in New York State. *J Dairy Sci* 1996;79:1040-1049.
3. Donovan GA, Dohoo IR, Montgomery DM, et al. Calf and disease factors affecting growth in female Holstein calves in Florida, USA. *Prev Vet Med* 1998;33:1-10.
4. Extralabel drug use in animals. 21 CFR 530.
5. FDA. Guidance for Industry #207. Studies to evaluate the metabolism and residue kinetics of veterinary drugs in food-producing animals: marker residue depletion studies to establish product withdrawal periods. March 2015. Available at: www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM207941.pdf. Accessed Jul 23, 2016.
6. FDA. Guidance for Industry #191. Changes to approved NDAs—new NDAs vs category II supplemental NDAs. May 2015. Available at: www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052460.pdf. Accessed Jan 20, 2016.
7. Stobo IJ, Roy JH, Gaston HJ. Rumen development in the calf. 2. The effect of diets containing different proportions of concentrates to hay on digestive efficiency. *Br J Nutr* 1966;20:189-215.
8. Drackley JK. Calf nutrition from birth to breeding. *Vet Clin North Am Food Anim Pract* 2008;24:55-86.
9. Toutain PL, Ferran A, Bousquet-Mélou A. Species differences in pharmacokinetics and pharmacodynamics. In: Cunningham F, Elliott J, Lees P eds. *Comparative and veterinary pharmacology*. Berlin, Germany: Springer-Verlag, 2010;19-48.
10. Brown SA, Chester ST, Robb EJ. Effects of age on the pharmacokinetics of single dose ceftiofur sodium administered intramuscularly or intravenously to cattle. *J Vet Pharmacol Ther* 1996;19:32-38.
11. Kissell LW, Brinson PD, Gehring R, et al. Pharmacokinetics and tissue elimination of flunixin in veal calves. *Am J Vet Res* 2016;77:634-640.
12. Gips M, Soback S. Norfloxacin nicotinate pharmacokinetics in unweaned and weaned calves. *J Vet Pharmacol Ther* 1996;19:130-134.
13. Kaartinen L, Pyörälä S, Moialen M, et al. Pharmacokinetics of enrofloxacin in newborn and one-week old calves. *J Vet Pharmacol Ther* 1997;20:479-482.
14. Nouws JF, Vree TB, Degen M, et al. Pharmacokinetics of sulphamethoxazole in calves and cows. *Vet Q* 1991;13:10-15.
15. Lichtenwalner DM, Cameron BD, Young C. The metabolism and pharmacokinetics of flunixin in cows and steers, in *Proceedings*. 14th World Cong Dis Cattle 1986; 1179-1183.
16. Waxman Dova S, Albarellos G, Kreil V, et al. Comparative pharmacokinetics of an injectable cephalixin suspension in beef cattle. *Res Vet Sci* 2008;85:570-574.
17. Riviere JE. Principles of drug movement in the body. In: Riviere JE, ed. *Comparative pharmacokinetics: principles, techniques and applications*. 2nd ed. Ames, Iowa: Wiley-Blackwell, 2011;13-25.
18. Ionescu C, Caira MR. Pathways of biotransformation—phase I reactions. In: *Drug metabolism: current concepts*. Dordrecht, The Netherlands: Springer Netherlands, 2005;41-128.
19. Gibson GG, Skett P. Pathways of drug metabolism. In: *Introduction to drug metabolism*. 3rd ed. Cheltenham, England: Nelson Thornes Ltd, 2001:1-37.
20. Shoaf SE, Schwark WS, Guard CL, et al. The development of hepatic drug-metabolizing enzyme activity in the neonatal calf and its effect on drug disposition. *Drug Metab Dispos* 1987;15:676-681.
21. Schwark WS. Factors that affect drug disposition in food-producing animals during maturation. *J Anim Sci* 1992;70:3635-3645.
22. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part I. *Clin Pharmacokinetics* 2002;41:959-998.
23. Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants: part II. *Clin Pharmacokinetics* 2002;41:1077-1094.
24. Fernandez E, Perez R, Hernandez A, et al. Factors and mechanisms for pharmacokinetic differences between pediatric population and adults. *Pharmacokinetics* 2011;3:53-72.

25. Wrenn TR, Cecil HC, Connolly MR, et al. Extracellular body water of growing calves as measured by thiocyanate space. *J Dairy Sci* 1962;45:205-209.
26. Sekine J, Fujita K, Asahida Y. A prediction of body water compartments of growing cattle in vivo. *Asian Aust J Anim* 1992;5:7-11.
27. Toutain PL, Bousquet-Mélou A. Volumes of distribution. *J Vet Pharmacol Ther* 2004;27:441-453.
28. Monti DJ. AMDUCA regulates small and large animal practice. *J Am Vet Med Assoc* 2000;216:1889.
29. FDA. Guidance for industry #3. General principles for evaluating the human food safety of new animal drugs used in food-producing animals. Draft revised guidance. July 2016. Available at: www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm052180.pdf. Accessed Dec 13, 2016.
30. USDA Food Safety and Inspection Service. Screening and confirmation of animal drug residues by UHPLC-MS-MS Available at: www.fsis.usda.gov/wps/wcm/connect/b9d45c8b-74d4-4e99-8eda-5453812eb237/CLG-MRM1.pdf?MOD=AJPERES. Accessed Sep 26, 2016.
31. FARAD. Extralabel drug use (ELDU) resource page. Available at: www.farad.org/eldu/eldumain.asp. Accessed Dec 14, 2016.
32. North American Compendiums Inc. Compendium of veterinary products (CVP) electronic database. Available at: bayer-all.naccvp.com/?u=bayer&p=dvm. Accessed Dec 14, 2016.
33. FDA. Animal drugs @ FDA. Available at: www.accessdata.fda.gov/scripts/animaldrugsatfda/details.cfm?dn=140-338. Accessed Dec 14, 2016.
34. Vetgram FARAD. Available at: www.farad.org/vetgram/search.asp. Accessed Dec 14, 2016.
35. USDA National Animal Health Monitoring System. Dairy 2014. Dairy Cattle Management Practices in the United States, 2014. Available at: www.aphis.usda.gov/animal_health/nahms/dairy/downloads/dairy14/Dairy14_dr_PartI.pdf. Accessed Dec 14, 2016.
36. Smith G. Antimicrobial decision making for enteric diseases of cattle. *Vet Clin North Am Food Anim Pract* 2015;31:47-60.
37. New animal drugs for use in animal feeds; oxytetracycline; neomycin. 21 CFR 558.
38. USDA Food Safety and Inspection Service. United States national residue program for meat, poultry, and egg products. 2014 residue sample results. Available at: www.fsis.usda.gov/wps/wcm/connect/2428086b-f8ec-46ed-8531-a45d10bfef6f/2014-Red-Book.pdf?MOD=AJPERES. Accessed Dec 13, 2016.
39. Paige JC, Pell F. Drug residues in food producing animals. *FDA Veterinarian* 1997;12.
40. Rangel-Lugo M, Payne M, Webb AI, et al. Prevention of antibiotic residues in veal calves fed colostrum. *J Am Vet Med Assoc* 1998;213:40-42.
41. Musser JM, Anderson KL, Rushing JE, et al. Potential for milk containing penicillin G or amoxicillin to cause residues in calves. *J Dairy Sci* 2001;84:126-133.
42. Musser JM, Anderson KL, Boison JO. Tissue disposition and depletion of penicillin G after oral administration with milk in unweaned dairy calves. *J Am Vet Med Assoc* 2001;219:346-350.
43. Guest GB, Paige JC. The magnitude of the tissue residue problem with regard to consumer needs. *J Am Vet Med Assoc* 1991;198:805-808.
44. Hausler K, Godden SM, Schneider MJ, et al. Hot topic: investigating the risk of violative meat residues in bob veal calves fed colostrum from cows treated at dry-off with cephalixin benzathine. *J Dairy Sci* 2013;96:2349-2355.
45. Adulterated drugs and devices. 21 CFR 501(a)(6) § 351(a)(6).
46. FDA. Department of Health and Human Services: Warning letter #15-PHI-09. Available at: www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm432140.htm. Accessed Jan 12, 2017.
47. FDA. Veterinary feed directive. *Fed Regist* 2015;80:31708-31735.
48. California State Legislature. SB-27. Hill. Livestock: use of antimicrobial drugs. Available at: leginfo.ca.gov/faces/billTextClient.xhtml?bill_id=201520160SB27. Accessed Jul 25, 2016.
49. Romvary A, Sandor G. Distribution and elimination of sulfamethoxazole and N4-sulfamethoxazole in calf and piglet tissues. *Acta Vet Scand Suppl* 1991;87:432-433.
50. Meijer LA, Ceyskens KG, de Jong WT, et al. Correlation between tissue and plasma concentrations of oxytetracycline in veal calves. *J Toxicol Environ Health* 1993;40:35-45.
51. Luthman J, Jacobsson SO. The availability of tetracyclines in calves. *Nord Vet Med* 1983;35:292-299.
52. Nouws JF, van Ginneken CA, Ziv G. Age-dependent pharmacokinetics of oxytetracycline in ruminants. *J Vet Pharmacol Ther* 1983;6:59-66.
53. Webster HB, Morin D, Jarrell V, et al. Effects of local anesthesia and flunixin meglumine on the acute cortisol response, behavior, and performance of young dairy calves undergoing surgical castration. *J Dairy Sci* 2013;96:6285-6300.
54. Mintline EM, Varga A, Banuelos J, et al. Healing of surgical castration wounds: a description and an evaluation of flunixin. *J Anim Sci* 2014;92:5659-5665.
55. Paull DR, Small AH, Lee C, et al. Effect of local infusion of NSAID analgesics administered alone or in combination on the pain associated with band castration in calves. *Aust Vet J* 2015;93:271-277.
56. Sidhu PK, Gehring R, Mzyk DA, et al. Avoiding violative flunixin meglumine residues in cattle and swine. *J Am Vet Med Assoc* 2017;250:182-189.
57. Glynn HD, Coetzee JF, Edwards-Callaway LN, et al. The pharmacokinetics and effects of meloxicam, gabapentin, and flunixin in postweaning dairy calves following dehorning with local anesthesia. *J Vet Pharmacol Ther* 2013;36:550-561.
58. Battaller N. FDA communication regarding the use of meloxicam in cattle. Available at: www.aabp.org/members/resources/FDA_Communication_meloxicam_AMDUCA_7.2014.pdf. Accessed Dec 14, 2016.
59. AVMA. AMDUCA extralabel drug use algorithm. Available at: www.avma.org/KB/Resources/Reference/Pages/AMDUCA2.aspx. Accessed Dec 14, 2016.
60. Coetzee JF, Mosher RA, Griffith GR, et al. Pharmacokinetics and tissue disposition of meloxicam in beef calves after repeated oral administration. *J Vet Pharmacol Ther* 2015;38:556-562.
61. European Medicines Agency. Annex 1. Summary of product characteristics. Metacam. Available at: www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/veterinary/000033/WC500065777.pdf. Accessed Jul 25, 2016.
62. FDA. Cephalosporin order of prohibition goes into effect. Available at: www.fda.gov/AnimalVeterinary/NewsEvents/CVMUpdates/ucm299054.htm. Accessed Dec 14, 2016.
63. Drugs prohibited for extralabel use in animals. 21 CFR 530.41.
64. Woodrow JS, Caldwell M, Cox S, et al. Comparative plasma pharmacokinetics of ceftiofur sodium and ceftiofur crystalline-free acid in neonatal calves. *J Vet Pharmacol Ther* 2016;39:271-276.
65. Foster DM, Jacob ME, Warren CD, et al. Pharmacokinetics of enrofloxacin and ceftiofur in plasma, interstitial fluid, and gastrointestinal tract of calves after subcutaneous injection, and bactericidal impacts on representative enteric bacteria. *J Vet Pharmacol Ther* 2016;39:62-71.
66. Merck Animal Health. Nuflor (florfenicol) product label. Madison, NJ: Merck Animal Health Intervet Inc, 2011.
67. FDA. Extralabel animal drug use; fluoroquinolones and glycopeptides; order of prohibition. *Fed Regist* 1997;62:27944-27947.
68. Zoetis. Advocin (danofloxacin injection) product label. Kalamazoo, Mich: Zoetis Inc, 2014.
69. Bayer. Baytril (enrofloxacin) product label. Shawnee Mission, Kan: Bayer Healthcare LLC, 2015.
70. Tolerances for residues of new animal drugs in food. 21 CFR 556.