FARAD Digest

Update on FARAD food animal drug withholding recommendations

Scott R. R. Haskell, DVM, MPVM; Ronette Gehring, BVSc, MMedVet; Michael A. Payne, DVM, PhD; Arthur L. Craigmill, PhD; Alistair I. Webb, BVSc, PhD, DACVA; Ronald E. Baynes, DVM, PhD; Jim E. Riviere, DVM, PhD

Recently published pharmacokinetic studies and new drug approvals have made it possible and necessary to update the previously published **Food Animal Residue Avoidance Databank (FARAD)** extralabel **withdrawal interval (WDI)** recommendations for pharmaceuticals administered to food-producing animals. A label **withdrawal time (WDT)** is established by the FDA Center for Veterinary Medicine when a drug is approved for use in a food animal.[1] Adherence to the label WDT ensures that tissues or products taken from the treated animal will not contain residues in excess of the official tolerance. Extralabel WDIs are a specific FARAD recommendation delineating the withholding time necessary to ensure that violative residues of a drug will not be detectable in tissues or products following extralabel use. FARAD recommendations for WDIs are based on pharmacokinetic data analysis, foreign and domestic label WDTs, and **maximum residue limits (MRLs)**. A patented algorithm for calculating WDIs (the Extrapolated Withdrawal Estimator) is also being implemented and validated. The purpose of this FARAD Digest is to update the FARAD WDIs so that practitioners may have the most current information on which to base extralabel drug use in food animals.

Acepromazine Maleate

Acepromazine maleate is not labeled for use in any food animal in the United States, but is labeled in Canada and Australia. Previously, the FARAD extralabel WDI recommendations for acepromazine in swine were derived exclusively from foreign approvals. The most conservative of these foreign labels is the one Canada has for cattle, goats, sheep, pigs, and horses, where it may be administered at a dose up to 0.055 mg/kg (0.025 mg/lb), IV, or up to 0.44 mg/kg (0.2 mg/lb), IM, with 7-day slaughter and 48-hour milk WDTs. Neither Canada nor Australia has established an MRL (similar to a tolerance in the United States) for the drug despite its approved food animal uses in those countries. However, one residue depletion study[2] supports the Canadian label slaughter WDT of 7 days for swine when acepromazine is administered at up to 0.13 mg/kg (0.06 mg/lb), IM. Because of the complete absence of residue and pharmacokinetic data for other food animal species, FARAD cannot make WDI recommendations for other species at this time.

Flunixin Meglumine

Flunixin meglumine is not labeled for use in lactating dairy cattle in the United States. On the basis of published milk residue depletion studies,[3] FARAD recommends an extralabel milk WDI of 72 hours and a slaughter extralabel WDI of 4 days following doses of up to 2.2 mg/kg (1 mg/lb), IV.[3] Flunixin should not be given IM or SC because of excessive injection site lesions and the prolonged tissue clearance.

Nitrofurazone

Effective May 7, 2002, the FDA prohibited use of all nitrofuran-containing drugs in food-producing animals. This prohibition includes topical applications of nitrofuran puffer and wound spray products.

Oxytetracycline in Lactating Cattle

Previously, FARAD recommended extralabel milk WDI of 196 hours for dairy cattle receiving a sustained release oxytetracycline product at a dose of 20 mg/kg (9 mg/lb). In 1998, 1 product received a label addition for lactating dairy cattle that permits milk from treated cows to be marketed 96 hours after a single IM or SC injection. With this approval, the **US FDA Center for Veterinary Medicine (USFDA/CVM)** concurrently established the first US tolerance for tetracyclines in milk. The cow-milk tolerance of 0.3 ppm is based on the sum of all tetracycline family residues detected in a sample.

For extralabel use of oxytetracycline by intrauterine administration, FARAD has recommended a 168-hour milk WDI after doses up to 2 g. Several studies[4-6] have been published on intrauterine use of tetracycline in cattle, and these studies suggest that after administration of up to 2 g of oxytetracycline, a 72-hour extralabel withdrawal period will allow milk residues to deplete to less than the newly established tolerance.

From FARAD, Department of Environmental Toxicology, College of Agricultural and Environmental Sciences, University of California, Davis, CA 95616 (Haskell, Payne, Craigmill); FARAD, Center for Chemical Toxicology Research and Pharmacokinetics, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606 (Gehring, Baynes, Riviere); and FARAD, College of Veterinary Medicine, University of Florida, Gainesville, FL 32610-0136 (Webb).

Address correspondence to Dr. Haskell.

These milk WDIs apply only to aqueous formulations of oxytetracycline. FARAD recommends testing milk after extralabel intrauterine administration, as there is interindividual variability in the residue elimination profiles in milk. On the basis of US and foreign label WDTs, FARAD recommends an extralabel slaughter WDI of 28 days for such intrauterine treatment.

Oxytetracycline in Other Species

There are no USFDA/CVM-approved injectable oxytetracycline products for use in sheep or goats. The **Animal Medical Drug Use Clarification Act of 1994 (AMDUCA)** authorizes veterinarians to use veterinary or human pharmaceuticals in an extralabel manner.[2] Practitioners prescribing extralabel treatment are required to establish an extralabel WDI sufficient to ensure that harmful residues do not develop in food products. Published pharmacokinetic and residue studies[7,8] of oxytetracycline funded by the USDA's Minor Use Animal Drug Program (National Research Support Program #7) have examined tissue depletion of oxytetracycline in sheep and goats following a single IM injection of a sustained release product at a dose of 20 mg/kg. These studies confirm that the slaughter WDT of 28 days for cattle will be adequate as a FARAD-recommended extralabel WDI for slaughtered sheep and goats. A milk WDI of 96 hours will be adequate for a 20-mg/kg dose administered IM or SC to lactating goats.[8]

For swine, it is noteworthy that in August 1996, the National Pork Producers Council called for producers supplying packers for international markets to voluntarily extend the label WDT from 7 days to 14 days following the administration of tetracycline products in feed or water to swine. This extension in the label WDT was recommended to ensure the residue concentrations will be below the MRLs of other countries, which may be lower than the US tolerance.

Phenylbutazone

On May 29, 2003, the FDA began prohibiting extralabel use of phenylbutazone in female dairy cattle ≥ 20 months of age. FARAD discourages the use of phenylbutazone in any food-producing animal because of its prolonged excretion.

Xylazine and Tolazoline

The previous FARAD slaughter WDI recommendation for use of xylazine in cattle (10 days) was based on foreign approvals and supported by serum pharmacokinetic data indicating a similar half-life and volume of distribution in all species studied. New Zealand recently approved use of xylazine in cattle, and the data acquired for this approval has provided more exacting milk and tissue depletion data. On the basis of these data, FARAD recommends a slaughter WDI of 4 days and milk WDI of 24 hours after IM administration of xylazine at 0.05 to 0.30 mg/kg (0.02 to 0.136 mg/lb) to cattle. Concurrently, New Zealand approved tolazoline as a xylazine reversal agent in cattle. Based on the product approval data, FARAD recommends WDIs of 48 hours for milk and 8 days for tissue when tolazoline is given IV at a dosage of 2.0 to 4.0 mg/kg (0.9 to 1.8 mg/lb) in cattle.

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