Food Animal Residue Avoidance Databank

07 February 2024
Dockets Management
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket No. FDA–2023–N–3168 Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Extralabel Drug Use in Animals

The directors and call responders of the US Food Animal Residue Avoidance Databank (US FARAD) program appreciate the opportunity to provide comment on the announced Agency information collection activities under OMB Control Number 0910–0325—Extension for 21 CFR 530 Extralabel Drug Use (ELDU) in Animals. US FARAD is a USDA-NIFA supported national program that constitutes several universities and has been providing scientifically based withdrawal intervals for food-producing animals since 1981. US FARAD serves to protect human health by being the primary expert source for veterinarians after ELDU drug use or contaminant exposure. Through the assimilation of a comprehensive drug database and the use of state-of-the-art pharmacokinetic modeling, US FARAD scientists determine appropriate withdrawal intervals for a wide array of chemical entities and provide this information to veterinarians free of charge through a toll-free call center as well as a publicly accessible web site.[1] In addition to US FARAD's rapid response assistance regarding extra-label use of drugs in animal agriculture, FARAD also consults with veterinarians and toxicologists during food contamination emergencies which might arise from accidental exposure to environmental toxins, particularly pesticides, or intentional efforts to contaminate the human food supply. As part of FARAD's mission, we strongly support the AMDUCA provisions that allow for extralabel use of FDA-approved human and animal drugs with veterinary oversight. ELDU is critical in veterinary practice to allow for the prevention, treatment, and control of diseases that lack effective FDA-approved treatments in food animals, thereby maintaining safe, efficient, and humane production practices.

Representing an organization whose mission is the evidence-based calculation of withdrawal intervals following ELDU, our comments will address the potential impacts of implementing the proposed framework for analytical method development on producers and veterinarians who oversee ELDU in food animals. Based on the proposed collection of information activities, we have several substantive concerns about the impacts of third-party analytical development for residue testing following ELDU in food animals.

Substantive Concern: An excessively long withdrawal interval may be necessary following third party development of a highly sensitive analytical methods, if the safe level assigned to tissue following ELDU in food animals is set to below the analytical method's limit of detection. ELDU withdrawal intervals to deplete below an analytical limit of detection are likely to substantially exceed the FDA approved withdrawal time for the labeled species.

From a FARAD perspective, the challenge in formulating a withdrawal interval recommendation lies in determining what safe concentration should be targeted following ELDU, and if there is sufficient

[1] http://www.farad.org/

residue depletion data with which to estimate a tissue depletion with a reasonable level of confidence. In Docket No. FDA–2023–N–3168, the Agency states that "Agency regulations in 21 CFR part 530, permit FDA, if we find that there is a reasonable probability that the extralabel use of an animal drug may present a risk to public health, to establish a safe level for a residue from the extralabel use of the drug, and to require the development of an analytical method for the detection of residues above that established safe level. This requirement is codified at 21 CFR 530.22(b)." As stated in 21 CFR 530.22(a), the Agency defines the processes for establishing a safe level, where the Agency can "(1) Establish a finite safe level based on residue and metabolism information from available sources; (2) Establish a safe level based on the lowest level that can be measured by a practical analytical method; or (3) Establish a safe level based on other appropriate scientific, technical, or regulatory criteria." However, the Agency has not defined which of the three criteria will be used to define the safe level applied to cases of extralabel drug use in food animals.

In Docket No. FDA–2023–N–3168, the Agency states: "Although to date, we have not established a safe level for a residue from the extralabel use of any new animal drug and, therefore, have not required the development of analytical methodology, we believe that there may be instances when analytical methodology will be required." Based on these statements and the regulations in 21 CFR 530.22(a), we are concerned that—in the absence of residue studies performed in the extralabel species to support an NADA or ANADA-- the Agency will apply the analytical limit of detection as the established safe level. Current analytical methods can detect drug residues to an extremely low limit of detection (LOD).

Substantive Concern: Based on these factors, we have concerns that the extremely low analytical LODs will be used in replacement of an adequate human food safety risk assessment resulting in undue burden on producers and ultimately less feasible options available for treatment of serious illness in minor species.

To provide an example, florfenicol is approved for use in beef and dairy cattle <20 months of age for the treatment of bovine respiratory disease. An acceptable daily intake (ADI) of florfenicol for all edible tissues has been established at 10 ug/kg bodyweight/day.[1] Therefore, extrapolating from this ADI, the Agency has set the tolerance (safe level) for florfenicol residues for the marker residue of florfenicol amine in the liver to be 3700 ppb.[2]

However, florfenicol is not approved for use in sheep and goats in the US, and therefore any use of this drug in small ruminants is considered extralabel. Florfenicol is FARAD's 5th most requested drug for withdrawal intervals following ELDU in goats in the US, where it is commonly used for the treatment of susceptible bacteria causing respiratory disease.[3] Since there is no established safe level/tolerance for florfenicol in goat matrices in the US, when FARAD is calculating a withdrawal interval recommendation following drug use in goats, we must ensure that florfenicol residues cannot be detected in any of the edible tissues/consumable fluids at the end of the withdrawal interval.

[1] 21 CFR 556.283(a)
[2] 21 CFR 556.283(b)(1)(i)
[3] Wu X, Lin Z, Toney E, et al. Pharmacokinetics, tissue residue depletion, and withdrawal interval estimations of florfenicol in goats following repeated subcutaneous administrations. Food Chem Toxicol. 2023;181:114098. doi:10.1016/j.fct.2023.114098

Based on the current FSIS methodology, the minimum applicability level (MLA) for florfenicol amine residues in cattle liver tissue is 300 ppb (0.3 ug/g).[1] However, a recently published study performed using a goat model validated an analytical method in accordance with the FDA Bioanalytical Method Validation Guidance for Industry for caprine tissues and established an LOD of 120 ppb for florfenicol amine in the liver.[3] This study used the same analytical method that was approved for bovine tissues and validated that analytical method for use in caprine tissues. In this study, based on common ELDU by US veterinarians, florfenicol was administered at 40 mg/kg subcutaneously every 96 hours for 2 doses in goats. The withdrawal interval calculated using the FDA method for the marker residue in the liver to deplete to below the safe level was 95 days when the cattle tolerance was applied, 173 days when the MLA was applied, and 202 days when the LOD was applied as the safe level for this minor species.[3] Since this study and analytical method validation was not part of seeking a minor species approval, the safe level applied for determining withdrawal intervals following ELDU of florfenicol in goats must be the analytical LOD—whereas a major species tolerance may be applied should a label claim be sought for goats.

From a US federal standpoint, the concern of increasingly sensitive analytical methods for labeled drug use in food animals has been addressed in 84 FR 32982, where new analytical methods other than the "'regulatory method' derived from the practicable method submitted by a sponsor as part of the new animal drug application can be used to determine the quantity of residue in edible tissues for surveillance and enforcement purpose."[2] In that response, the Agency stated that "an analytical method other than the practicable method can be used for surveillance and enforcement purposes for non-carcinogenic compounds. Such an analytical method should have the same capability as the practicable method to determine the quantity of the drug residues such that the tolerance, withdrawal period, or other use restrictions continue to ensure that the use of the drug will be safe. Therefore, the assigned withdrawal periods will not need to be changed."[5]

However, this statement only applies to new analytical methods developed to replace an existing approved sponsor-submitted analytical method for residue detection in an FDA approved labeled species. When creating a new analytical method for drug residue detection in matrices from species that are not listed on the FDA approved label (ELDU), there is no standardized analytical method, tolerance, or withdrawal period with which to compare the new analytical methodology. Therefore, we are seeking the following clarifications:

- In the development of new analytical methods for residue detection following ELDU, does the Agency intend to ensure that the new analytical method for matrices from extra label species has the same capability (LOD) as the established analytical methods for the FDA approved labeled species that have the closest physiology to the ELDU species?
- If not, then what criteria is the Agency using to establish the safe level for the drug in this extra label species?
    - The Agency might consider that safe levels are based on lifetime consumption of matrices at a regular consumption rate to establish the Allowable Daily Intake (ADI) but consumption of ELDU matrices may be limited except for certain cultural groups.

[1] USDA FSIS. 2021. Determination and Confirmation of Florfenicol. CLG-FLOR1.06
[2] New Animal Drugs; Updating Tolerances for Residues of New Animal Drugs in Food. 84 FR 32982 (July 11, 2019)

- Must all analytical methods developed to test for drug residues following ELDU in food animals be in accordance with the FDA Bioanalytical Method Validation Guidance for Industry?
    - The Agency may consider that, while drug sponsor and FSIS methods are developed in accordance with the method validation GFI, many methods developed by university researchers, state/federal diagnostic laboratories, or private laboratories do not undergo the rigorous validation procedures described in the Bioanalytical Method Validation GFI.

In GFI #61, the Agency stated that "In some instances, the tolerance for a drug approved for use in a food-producing species may be appropriate for extrapolation to the same drug for use in a food-producing minor species."[1] However, there is currently a lack of clarity if this approach will be considered in determining the safe level following ELDU in minor species. For example, in the case of florfenicol, if the goat specific analytical method LOD is applied as the safe level, the producer must bear the expense of an extra 29-107 days of feed, husbandry, and veterinary costs compared to withdrawal intervals targeting the cattle tolerance or cattle FSIS MLA[2]—significantly reducing the already slim margins on commercial goat production. Additionally, considering that the most profitable market for meat goats in the US is for market kids <60 pounds bodyweight, or between 3-9 months of age,[3,4] a 202-day meat withdrawal interval would effectively eliminate the producer's return on investment for any treated animal—preventing any practicable extra label use of this drug in market animals. FARAD prioritizes human food safety but encourages the Agency to not target overly conservative approaches so that small producers are not outcompeted by exports. In addition, other global agencies (such as EMEA) utilize a species grouping approach for establishing safe levels which might be considered as a potential approach for the US.

Considering the shortage of veterinarians entering into food animal practice[5], it is not surprising that 50.2% of goat operations had not consulted a veterinarian in the past year[6], and that only 10.5% of goat operations that used antibiotics had consulted a veterinarian for a withdrawal recommendation.[8] In order to effectively engage with producers and maintain compliance, veterinarians need to be able to provide optimal treatment strategies to all food-producing species that are cost-effective, safe, and have reasonable withdrawal intervals that are driven by a human food safety risk assessment. Therefore, we strongly urge the Agency to consider practicable methods rooted in human food safety risk assessment and based on exposure following ELDU, rather than chasing an analytical LOD for determining safe levels when developing analytical methods to test for drug residues following ELDU in food animals.

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[1] GFI #61: Special Considerations, Incentives, and Programs to Support the Approval of New Animal Drugs for Minor Uses and for Minor Species. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cvm-gfi-61-special-considerations-incentives-and-programs-support-approval-new-animal-drugs-minor

[2] Wu X, Lin Z, Toney E, et al. Pharmacokinetics, tissue residue depletion, and withdrawal interval estimations of florfenicol in goats following repeated subcutaneous administrations. Food Chem Toxicol. 2023;181:114098. doi:10.1016/j.fct.2023.114098

[3] https://www.fsis.usda.gov/food-safety/safe-food-handling-and-preparation/meat/goat-farm-table

[4] https://www.ams.usda.gov/market-news/goat-reports

[5] https://www.nifa.usda.gov/vmlrp-map

[6] USDA. 2022. Goat 2019, "Part I: Reference of Goat Management Practices in the United States, 2019" USDA–APHIS–VS–CEAH–NAHMS. Fort Collins, CO#792.0821

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We thank FDA for the opportunity to provide our comments and questions. For any questions regarding these comments, please contact Dr. Lisa Tell at latell@ucdavis.edu.

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