FARAD: How we respond to withdrawal inquiries

F. Maunsell*, BVSc, PhD, DACVIM; R. Baynes2, DVM, PhD; J. Davis3, DVM, PhD; D. Foster2, DVM, PhD, DACVIM; M. Jaberi-Douraki4, PhD; Z. Lin1, BMVSc, PhD, DABT, CPH; J. Riviere2, DVM, PhD, DACVCP; L. Tell5, DVM, DABVP (Avian), DACZM

1University of Florida, Gainesville, FL 32608;
2North Carolina State University, Raleigh, NC 27607;
3Virginia-Maryland College of Veterinary Medicine, Blacksburg, VA 24061;
4Kansas State University, Manhattan, KS 66506,
5University of California-Davis, Davis, CA 95616

Abstract
The Food Animal Residue Avoidance and Depletion (FARAD) program is a USDA-funded, national food safety and residue-avoidance program housed at 5 universities. FARAD performs a broad array of functions centered on the collection, evaluation, analysis, interpretation and dissemination of information related to the depletion of drugs and other chemicals in food animals. A key service offered by FARAD is the provision of advice on appropriate withdrawal intervals (WDI) following extralabel drug (ELDU) administration to food animals by veterinarians, in compliance with the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA). Professional FARAD staff at 3 call centers respond to WDI requests, where they utilize a comprehensive databank of pharmacokinetic data together with tools ranging from simple to complex models for the accurate estimation of safe WDIs. In complex cases, such as those involving large numbers of animals or mathematical modeling, a FARAD directors/advisory group reviews the WDI advice. In some circumstances, such as ELDU specifically prohibited by FDA, FARAD is unable to provide a WDI. However, in all cases, FARAD strives to provide veterinarians with scientifically sound, current residue avoidance advice following ELDU or chemical exposure of food animals, within the provisions of the AMDUCA regulations.

Key words: FARAD, extralabel drug use, residue, withdrawal interval

Introduction
The Food Animal Residue Avoidance and Depletion (FARAD) program has been a U.S. congress-authorized, USDA-funded national food safety program since 1982. This program is coordinated and delivered in a collaborative manner by faculty and staff at several U.S. land-grant universities. There are currently five FARAD program centers, at University of California at Davis, Kansas State University, Virginia-Maryland College of Veterinary Medicine, North Carolina State University, and the University of Florida. FARAD was established to help mitigate drug and chemical residues in food products, and our mandate is to support food animal veterinarians and other animal industry professionals in their responsibilities to ensure that animal products are safe for human consumption. FARAD is tasked with providing a portal for drug residue information, providing veterinarians with withdrawal advice for extralabel drug use (ELDU) while complying with the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) and its subsequent modifications, and providing withdrawal advice when food animals are accidentally exposed to chemicals or environmental contaminants. Throughout more than 3 decades of delivering this program, FARAD has continued to develop increased sophistication with respect to (1) acquisition and cataloging of pharmacokinetic data and comprehensive information resources, (2) adapting efficient mechanisms for information delivery and outreach to target audiences, and (3) utilizing complex quantitative tools and models for accurately estimating safe withdrawal intervals for a wide array of drugs and chemicals in nearly all species of domestic food animals. Where data to estimate withdrawal intervals is lacking for important food animal drugs or drug/species combinations, FARAD centers undertake in vivo research and development of new models. Pharmacokinetic data and models from this original research are then utilized to better estimate safe withdrawal intervals (for example, models for oxytetracycline depletion in small ruminants, or flunixin in a variety of species). The body of literature produced by FARAD comprises over 120 scientific publications that address various aspects of residue avoidance in food-producing animals.

FARAD services
All FARAD resources are available at our publicly accessible website (www.farad.org). In recent years, the majority of the information accessible at www.farad.org has been translated so that it is now available in both English and Spanish language versions.

Residue avoidance for FDA-approved animal drug use
One major programmatic function of FARAD is the collection, updating and dissemination of regulatory information pertaining to FDA-approved animal drugs. This data can be accessed using FARAD’s Veterinarians Guide to Residue Avoidance Management (VetGRAM), which is available as a web-based program and as an application for mobile devices. These FARAD products provide complete information about FDA-approved animal drugs, including dosing information, approved disease indications, species and use-class restrictions as well as the associated withholding times for meat, milk, eggs, honey and other products. A calendar function has been integrated into these programs to aid in the determination of proper withholding times and dates. Updated versions of the VetGRAM apps for mobile devices are currently under development and planned for release by the end of 2021.
**Withdrawal interval recommendations for extralabel drug use**

The FDA-approved withdrawal (or withholding) time (WT) is the period following the administration of an FDA-approved animal drug, in accordance with label guidelines, for which the animal and its products must be withheld from food production. The WT represents the period after which the concentrations or a drug or its metabolites in tissues or other animal products, fall below the FDA-established tolerance level (the concentration that FDA has determined is safe for human consumption). As distinct from the FDA-approved WT, veterinarians practicing ELDU are required to “establish a substantially extended withdrawal interval prior to marketing of milk, meat, eggs, or other edible products supported by appropriate scientific information.” A withdrawal interval (WDI), provided by FARAD, is the time following ELDU until drug concentrations in tissues or animal-derived products are estimated to fall below the FDA tolerance, if there is a tolerance established for that species/animal class/drug/matrix combination, or to undetectable concentrations (or the FSIS analytical limit of detection for the marker residue, drug or metabolites) if no tolerance is established. Note that when a drug is administered to a food animal species or class for which it is not approved, tolerances have not been established for acceptable residues of that drug or its metabolites in meat or other products of treated animals. In those circumstances, detection of any residue in products marketed for human consumption is considered a violation and subject to regulatory action (i.e. the tolerance is zero for the drug or its metabolites in meat or other products).

FARAD provides residue avoidance advice for veterinarians practicing ELDU in food animals through 1) general educational resources on the [www.farad.org](http://www.farad.org) website, 2) a WDI lookup tool, which contains WDI recommendations from FARAD Digest publications for selected ELDU in cattle, swine, goats and sheep and, 3) expert-mediated responses to individual requests for WDI advice from veterinarians submitted via a nationwide toll-free hotline (1-888-USFARAD or 1-888-873-2723) or through a web-based online submission portal, [http://cafarad.ucdavis.edu/FARMWeb/](http://cafarad.ucdavis.edu/FARMWeb/) (link on the FARAD homepage, [www.farad.org](http://www.farad.org)). In 2020, FARAD addressed 3,926 specific inquiries that directly involved 10.8 million animals, representing a 4.2% increase in requests over 2019 and reflecting a long-term trend of increasing demand for this service.

**Other resources on residue avoidance**

The FARAD website has links to a number of species- or topic-specific web pages which provide resources for users with specific interests. Examples include information on drug use in backyard poultry, bees, small ruminants and other species, the FDA’s prohibited and restricted drug/drug classification list; resources on Veterinary Feed Directives; links to FARAD Digests, which are summary or review documents published in *JAVMA* that address pertinent issues of residue avoidance in food animals; and a Bibliographic citations lookup tool, which is a searchable database of documents or references containing time versus drug concentration data from live animals. A recent addition to FARAD web-based resources has been a Commercial Drug Residue Screening Test (Rapid Assay) database of drug residue screening assays commercially available in North America ([https://cafarad.ucdavis.edu/RapidAssay/rapidassay.aspx](https://cafarad.ucdavis.edu/RapidAssay/rapidassay.aspx)); the database is searchable by species/drug/matrix combinations, and includes the sensitivity of the test and the FDA tolerance for that drug.

**How FARAD responds to requests for WDI advice**

Requests for WDI advice that are submitted online or via the hotline are answered at one of the three FARAD call centers (at UC-Davis, NC State, and VM Colleges of Veterinary Medicine) on a rotating schedule. Trained, doctoral-level professional FARAD staff members respond to requests, supervised by the FARAD director at their respective institution.

Initial screening is undertaken to determine if the request is consistent with AMDUCA guidelines for ELDU. Under AMDUCA, only a licensed veterinarian with a valid veterinary client-patient relationship can use and prescribe drugs in an extralabel manner. Requests for a WDI for ELDU from someone other than a veterinarian will not be processed; the person who submitted the request is advised to have their veterinarian contact us. If they do not have a veterinarian, they might consider contacting the closest college of veterinary medicine, Extension veterinarian, or the state veterinarian. FARAD does endeavor to provide WDI advice to producers or other industry professionals dealing with accidental exposure of food animals to environmental contaminants or chemicals, although we strongly encourage veterinary involvement in these cases. Requests are also screened to make sure that they do not entail ELDU prohibited by FDA; such requests are referred to the FARAD directors/advisory group. FARAD is only able to answer requests for withdrawal advice from within the U.S.

Following the initial screening of requests, the next step is to determine whether data exists on which to base a WDI estimation. Steps undertaken here include a review of relevant prior responses, as well as a FARAD database search for information on this species/animal class, drug, tolerances, target organ or matrix, half-life in the target organ, marker residues, and limit of detection for regulatory analytical methods. The data in the database originates from FARAD’s own research, from published data in the scientific literature, new drug approval applications, and numerous other sources. The database is compiled and maintained at UC-Davis, where relevant data on drug and chemical depletion in food animal species is extracted from its source, modeled, and entered into a computer-based archival database that is readily searchable for customized information retrieval. Because many factors can influence how rapidly an animal eliminates a chemical residue, information about diet, age, gender, breed and disease status are taken into consideration. Responders also search FARAD’s bibliographic database for other relevant information. When there is little or no data available through the above resources, responders search foreign drug approvals databases and recent documents available under the Freedom of Information Act associated with applications for drug approvals. AMDUCA stipulates that the withdrawal interval established by the veterinarian following ELDU must be supported by appropriate scientific information. If there is no relevant data available on which to estimate a WDI for the drug or chemical in question, then FARAD is unable to provide an estimated WDI.

Once relevant data have been obtained by FARAD responders, the next step is the prediction of tissue depletion of the drug. In certain situations, this may involve the use of simple mathematical extrapolations to predict tissue depletion of drugs or chemicals. In other situations, especially when less applicable information is available, the extrapolation process may necessitate the use of novel models with complex algorithms in order to predict depletion profiles.
Following the prediction of drug depletion profiles, recommendations for a WDI are finalized. How conservative a WDI recommendation is depends on a number of factors, including the strength of the data on which the WDI is formulated (for example, whether data is available for this species-drug combination versus extrapolation from a related species or a related drug), the number of treated or exposed animals, and the potential human health consequences of a residue. The response may include recommendations for use of a rapid detection assay for drug residues when the drug is of high regulatory concern, when there is very limited data on which to estimate a WDI, or when the dose and/or duration of drug administration are far beyond the range of existing depletion data profiles. In certain cases, responses are reviewed by the entire FARAD directors and science advisory group. This includes all requests involving large numbers of animals, prohibited drug use, carcinogenic drugs or chemicals, compounding, cases where there are substantial differences between methods of estimation or between the current estimated WDI and prior responses, and all accidental chemical or environmental toxin exposure cases.

In addition to cases where there is no data on which to base a WDI estimation, there are several circumstances in which FARAD responders are unable to provide WDI advice. FARAD’s mandate requires that we do not promote illegal ELDU, and we are not able to provide a WDI for ELDU specifically prohibited by FDA (https://www.fda.gov/animal-veterinary/resources-you/ins-and-outs-extra-label-drug-use-animals-resource-veterinarians#prohibited). In rare cases of accidental administration of a drug that is approved for use in food animals, but has specific ELDU restrictions that were violated, FARAD may be able to provide withdrawal advice. Similarly, FARAD does not provide WDI for carcinogenic or mutagenic drugs that are not FDA-approved for use in food animals. Because each case of ELDU represents a unique set of conditions that can affect WDI estimations, FARAD does not provide WDI for long lists of drugs for the purposes of protocol building. We do recognize, however, that veterinarians may wish to compare WDI advice among several different drug options when considering ELDU for a particular animal; it is helpful if the veterinarian can state that as their goal when submitting the request.

The FARAD WDI advice online submission form states that responses will generally be returned within 72 hours. In the case of simple requests, most responses are provided within 1-2 business days; complex cases often require more time, especially if the request is referred to the directors/advisory group for review. Responses consist of WDI advice and any testing recommendations or comments on the strength of data from which the WDI was formulated.

Reducing inconsistencies between responses is currently a high priority of the FARAD team. Responders are trained professionals who follow a standardized response algorithm. They all utilize the same databases and WDI calculation tools, and are supervised by the FARAD director at their respective institutions. In many cases, a change in WDI advice over time has a scientifically justifiable basis. New empirical pharmacokinetic data are constantly becoming available and are utilized to refine drug depletion calculations. This includes data from research that FARAD specifically undertakes to improve our understanding of the pharmacokinetics of important food animal drugs for which data is incomplete. In addition to new empirical data becoming available, new or updated models may have become available, allowing a more precise WDI estimation. Other changes that may have occurred between requests include changes in the tolerances or detection methods employed by regulatory agencies to detect drug residues. The same WDI advice may not be appropriate when there are differences in the animal description (e.g. ruminant versus pre-ruminant), drug formulation, route or frequency of administration, volume of drug per site, or co-administration of other drugs. A more conservative WDI may be issued when a large number of animals have been exposed or need to be treated, due to the relative risk of a violative residue.

In conclusion, FARAD provides veterinarians with scientifically sound, up-to-date, residue avoidance advice following drug use or chemical exposure of food animals, within the provisions of AMDUCA regulations. Veterinarians are reminded that FARAD is an advisory group and not a regulatory authority, and the prescribing veterinarian ultimately bears responsibility for any residues resulting from ELDU.

Acknowledgments
FARAD is a USDA-National Institute of Food and Agriculture-funded program.

References

