Guide to FARAD resources: historical and future perspectives

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The FARAD manages the Food Animal Residue Avoidance Databank and has been serving the veterinary profession for 35 years. It is funded and sponsored by the USDA National Institute of Food and Agriculture and is overseen and operated by faculty and staff within the colleges of veterinary medicine at the University of California-Davis, University of Florida, Kansas State University, and North Carolina State University.

The overarching goal of FARAD is to provide veterinary practitioners the most current and accurate information to facilitate the production of safe foods of animal origin through the prevention and mitigation of violative chemical (eg, drugs, pesticides, natural toxins, and environmental contaminants) residues in food animal products. The program has dramatically evolved since its inception in terms of data resources, outreach, quantitative tools used to estimate WDIs, precision of estimates, and methods implemented to disseminate information. With veterinarian inquiries increasing by double digits over the last several years, it is prudent to provide an overview of what FARAD can and cannot do and what it could do in the future.

Historical Background

The FARAD began its existence as a project within the USDA Cooperative Extension Service's Residue Avoidance Program in 1982. It was initially conceived as purely a database that would aggregate disparate sources of information on factors that could impact drug and chemical residues in the edible tissues of food-producing animals. Those data elements included approved drugs, pharmacokinetic data of drugs and chemicals, and rapid field-side residue assays. However, it soon became evident that many of those data sources simply did not exist in 1 location. At that time, there was no accurate catalog of approved drugs nor was there a compilation of tissue drug depletion data. The scarcity of such information resulted in the evolution of the original extension project into a research and outreach project that is an ideal example of a translational veterinary medicine program.

As FARAD collected data on FDA-approved drugs, it started publishing the *Comprehensive Compendium of Food Animal Drugs* in 1987, and even produced subset drug lists on the basis of individual production animal groups. Those subsets were distributed on request to veterinarians at the nominal costs of printing and postage. Hard copy distributions continued for about a decade until widespread access to computers and compact discs allowed data to be distributed, accessed, and downloaded electronically. In 1992, FARAD went live on the internet,[1] which enabled distribution of data via direct internet access to the VetGRAM database.

The program was often confronted with phone and internet queries from practitioners requesting information about what to do if a food animal was accidentally exposed to a pesticide or chemical or they needed to treat a food animal with a drug (generally an antimicrobial or other FDA-approved drug not approved for the specific indication or species) in an off-label, or extralabel, manner to improve treatment efficacy. This resulted in the establishment of the toll-free FARAD Hotline[a] in 1996 and initiated the outreach component of FARAD associated with the provision of recommendations for extended WDIs for drugs following extralabel administration to veterinarians. This re-

ABBREVIATIONS

ELDU	Extralabel drug use
FARAD	Food Animal Residue Avoidance and Depletion Program
MRL	Maximum residue limit
VetGRAM	Veterinarian's Guide to Residue Avoidance Management
WDI	Withdrawal interval
WDT	Withdrawal time

quired both professional judgement and access to data from the public domain (eg, peer-reviewed literature, conference abstracts, regulatory documents) regarding the rate and extent of drug and chemical depletion in food animals. Exhaustive literature searches were undertaken, often involving journals unrelated to veterinary medicine including those in analytical chemistry or food safety, to retrieve and generate time-concentration depletion rate data, which could then be analyzed with what we would now consider crude pharmacokinetic modeling techniques. Those efforts resulted in the publication of a series of handbooks of comparative pharmacokinetics and residues for veterinary antimicrobials,[2] therapeutic drugs,[3] and pesticides and environmental contaminates,[4] and finally a compiled version of all drug data from FARAD's extensive pharmacokinetic database available at that time.[5]

Those initial thrusts of gathering, compiling, and organizing data; refining mathematical modeling techniques; and providing outreach to veterinarians continued over the years and shaped how FARAD looks and operates today. Over time, dramatic increases in available data and users and advances in information technology have changed how FARAD gathers, analyzes, and distributes data. Additionally, the number of queries submitted to FARAD increased substantially after the US Congress passed the AMDUCA of 1994,[6] which made it legal for veterinarians to use drugs in an extralabel manner. Subsequently, the US Congress permanently authorized FARAD, albeit without permanent funding, in 1998 **(Figure 1)**.[7]

The Science Behind Estimating Extended Withdrawal Periods

Current FDA guidance

The fundamental, and what some might consider sole, mission of FARAD is to ensure that edible products from food-producing animals do not contain violative chemical or drug residues. For approved drugs, that endpoint is determined by WDTs established by regulatory agencies. In the United States, the WDT is defined as the time required after administration or exposure for a drug or chemical to deplete from the body of an animal to a concentration less than the legally established tolerance, which is the drug or chemical concentration that the FDA deems safe for human consumption. In regulatory jurisdictions other than the United States, the drug or chemical concentration that an FDA-equivalent regulatory agency considers safe for human consumption is typically referred to as the MRL. Often, the MRL for a specific drug or chemical is not the same as the tolerance established by the FDA.[8] In contrast to other pharmacological endpoints, the tolerance is a fixed number with variability related only to errors in the analytical method of detection used or actual time the sample was collected. The WDT must be valid for all types of animals that might be potentially treated with an approved drug; however, in the United States, the WDT is experimentally determined during the FDA drug-approval process and typically involves a small number (3 to 5) of healthy animals, which does not accurately reflect an individual animal within the population. Therefore, statistical inference must be used to calculate the WDT. Mathematically, the WDT is the point following administration of the labeled dosage of a drug after which there is 95% confidence that 99% of treated animals in the population will have tissue residues less than the tolerance for that drug **(Figure 2)**.[9] When a drug is administered in an extralabel manner, FARAD uses published scientific data and the established WDT to estimate an extended withdrawal period, or WDI. A rough guide relating tissue half-life to WDI is that a half-life multiplier of approximately 3 to 5 will estimate this population interval, although this can be very drug dependent.[10]

A common misconception is that the WDT for an approved drug relates to when the majority (> 50%) of that drug has been eliminated from the body. However, from a regulatory perspective, the WDT is the point in time after drug administration when tissue concentrations of that drug deplete to the tolerance. Because the tolerance is calculated on the basis of the amount of drug that is considered safe for human consumption independent of the disposition of that drug in the target species, the WDT does not indicate anything about the amount of drug remaining in a treated animal nor whether the pharmacokinetic processes have reached a steady state. It simply represents the best estimate of the time after drug administration when the tissues of treated animals are safe for human consumption. In fact, some drugs have a WDT of 0 hours. For milk and eggs, the WDT represents the duration after drug administration that milk or eggs must be discarded and not used for human consumption.

Estimation of an appropriate withdrawal period following administration of a drug or chemical to a food-producing animal involves 3 primary components: the dose of a drug or extent of exposure (amount, route, and duration) to a chemical, the duration required for the drug or chemical to be eliminated from the animal, and target tissue tolerance. It is generally assumed that when an approved drug is administered in accordance with the label, adherence to the labeled WDT will be sufficient to avoid violative tissue (or milk or egg) residues. In the vast majority of cases, that appears to be true unless disease processes or drug-drug interactions either prolong the elimination or alter the metabolic profile of a drug (eg, research[11–13] indicates administration of flunixin to dairy cows with severe mastitis can result in violative tissue and milk residues at the WDT). It is important to note that during the FDA drug-approval process, WDTs are determined on the basis of drug metabolism in healthy animals; however, drugs are generally administered to sick animals, and disease can alter and impair drug disposition and metabolism. For drugs that undergo extensive

SEC. 604. FOOD ANIMAL RESIDUE AVOIDANCE DATABASE PROGRAM.

(a) CONTINUATION OF PROGRAM. – The Secretary of Agriculture shall continue operation of the Food Animal Residue Avoidance Database Program (referred to in this section as the "FARAD program") through contracts, grants, or cooperative agreements with appropriate colleges or universities.

(b) ACTIVITIES. – In carrying out the FARAD program, the Secretary shall –

(1) provide livestock producers, extension specialists, scientists, and veterinarians with information to prevent drug, pesticide, and environmental contaminant residues in food animal products;

(2) maintain up-to-date information concerning –

(A) withdrawal times in FDA-approved food animal drugs and appropriate withdrawal intervals for drugs used in food animals in the United States, as established under section 512(a) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360b(a));

(B) official tolerances for drugs and pesticides in tissues, eggs, and milk;

(C) descriptions and sensitivities of rapid screening test for detecting residues in tissues, eggs, milk; and

(D) data on the distribution and fate of chemicals in food animals;

(3) publish periodically a compilation of food animal drugs approved by the Food and Drug Administration;

(4) make information on food animal drugs available to the public through handbooks and other literature, computer software, a telephone hotline, and the Internet;

(5) furnish producer quality-assurance programs with up-to-date data on approved drugs;

(6) maintain a comprehensive and up-to-date, residue avoidance database;

(7) provide professional advice for determining the withdrawal times necessary for food safety in the use of drugs in food animals; and

(8) engage in other activities designed to promote food safety.

(c) CONTRACT, GRANTS, AND COOPERATIVE AGREEMENTS. – The Secretary shall offer to enter into a contract, grant, or cooperative agreement with 1 or more appropriate colleges and universities to operate the FARAD program. The term of the contract, grant, or cooperative agreement shall be 3 years, with options to extend the term of the contract triennially.

(d) INDIRECT COSTS. - Federal funds provided to the Secretary under a contract, grant, or cooperative agreement under this section shall be subject to reduction for indirect costs of the recipient of the funds in an amount not to exceed 19 percent of the total Federal funds provided under the contract, grant, or cooperative agreement.

Figure 1—Copy of the US congressional authorization for FARAD.[7]

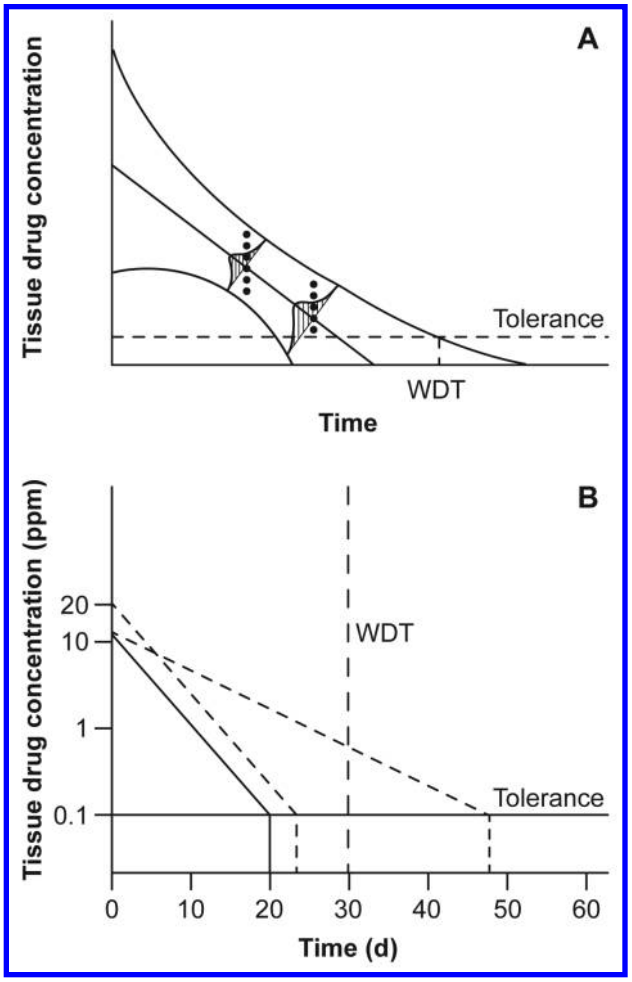

Figure 2—Graphical illustrations of the relationship between mean tissue decay of a drug or chemical residue and the WDT established by a regulatory agency such as the FDA (A) and the effect that doubling the dose or tissue half-life of a drug or chemical has on the WDT for a fixed tolerance (B). In panel A, the solid straight line represents the tissue concentration of a drug over time after administration, and the curved solid lines on either side of it represent the 95% confidence interval for the tissue drug concentration for 99% of the reference population. The horizontal dashed line represents the tolerance for that drug, and the vertical dashed line represents the WDT. Notice that the WDT is the point in time when the upper limit of the 95% confidence interval intersects with the tolerance. In panel B, the solid diagonal line represents the tissue concentration of a drug following administration of the labeled dosage, the solid horizontal line represents the tolerance, the vertical dashed line represents the WDT for the drug following administration of the labeled dosage, the dashed diagonal line that intersects the y axis at 20 ppm represents the tissue concentration of the drug following administration of twice the labeled dosage, and the dashed diagonal line that intersects the y axis at 10 ppm represents the tissue concentration of a drug when its tissue half-life is doubled. Notice that when the tissue half-life of the drug is doubled, the tissue drug concentration does not reach the tolerance until well after the labeled WDT. ppm = Parts per million.

metabolism, the established tolerance may not necessarily be for the parent (or unaltered) drug that was administered but instead may be for a marker residue (parent drug or metabolite), which reflects the total tissue concentration of the drug (unmetabolized parent drug and its metabolites).[14]

Estimation of WDIs following ELDU

When a drug is administered to an approved species in an extralabel manner (eg, the drug is administered at a higher dose than that provided on the label), the established tolerances remain the same, and the issue becomes how long the withdrawal period must be extended to allow tissue residues to deplete to concentrations below the tolerance following administration of the higher-than-labeled dose. Conceptually, this is a straightforward problem, which can be answered by the application of basic pharmacokinetic principles. For example, if the dose administered was twice the labeled dose, then the withdrawal period should be extended by 1 tissue half-life, because after 1 half-life, the doubled dose will be equivalent to the labeled dose, assuming the drug in question follows nonsaturated linear pharmacokinetics. In many cases, an additional half-life will be adequately accommodated by the labeled WDT (Figure 2). However, when a drug is administered to an animal with a disease process that impairs drug elimination, the rate of drug depletion in tissues may be prolonged, and a WDI longer than the labeled WDT may be required for tissue drug concentrations to deplete below established tolerances.

To estimate the WDI for a drug after ELDU, FARAD uses information regarding the pharmacokinetics of that drug in the species and tissue of interest. Tolerances are established for multiple critical tissues (eg, liver, kidney, muscle, and fat), and the depletion time for a drug may vary among those tissues. Physiologic changes associated with disease, age, or other factors that impair drug metabolism and elimination can have a greater impact on the time required for tissue drug concentrations to deplete below established tolerances than slight errors in the dose administered, which are often compensated for by the method used to calculate the labeled WDT (Figure 2).

Estimation of the WDI following ELDU is fairly straightforward when the drug is administered to an approved species (eg, only the dose or duration is altered) because information regarding the drug's disposition in that species generated for the FDA approval process is available, which allows for simple extrapolation strategies. However, more extensive pharmacokinetic data are required to estimate an appropriate WDI for a drug following administration to an unapproved species or by an unapproved route or when an unapproved drug is inadvertently used instead of an approved drug. In such instances, the primary approach involves the use of pharmacokinetic data obtained from published reports of drug or chemical concentrations in tissue over time after administration to determine tissue decay constants. It is important to note that those data represent the mean values for a small number of animals, and a discussion of how those data are used to estimate WDIs is beyond the scope of this digest but has been discussed elsewhere.[15–17] Early in FARAD's history,

pharmacokinetic models and computers were not sufficiently robust to allow complex calculations to be easily performed. As computer technology advanced, more complex pharmacokinetic modeling approaches were developed for human medicine.

Application of pharmacokinetic methods to estimate WDIs

A major research component of FARAD is the modification and adaptation of pharmacokinetic tools and models developed for human medicine to veterinary medicine, specifically for the purpose of residue avoidance. Those methods, which have proven invaluable to FARAD's mission, include mixed-effect (eg, population-based)[18–20] and physiologically based pharmacokinetic modeling.[14,21–24] In addition, when interspecies extrapolations are attempted, FARAD conducts large meta-analyses across the entire FARAD pharmacokinetic database to identify drugs that are well behaved on allometric analyses to provide some rational basis for extrapolation of data across species.[25,26] Well-behaved drugs are characterized primarily by first-order linear pharmacokinetics and are not extensively metabolized, which enable reliable extrapolations (eg, the half-life multiplier method previously discussed). Thus, pharmacokinetic principles are central to the interpretation of tissue deposition data and estimation of WDIs; the stronger the data, the more confident the prediction.

Tolerance versus MRL

Another approach used to estimate WDIs is to investigate whether the drug is approved for use for a similar condition in another country. In such an instance, the properties of the drug formulation approved for use in another country must be compared with those of the drug used in the scenario in question, and differences between the tolerance and MRL as well as the assumptions about food consumption used to calculate the MRL must be assessed to estimate an appropriate WDI.[17] Algorithms have been developed to convert the withdrawal period for drugs approved for use in foreign regulatory jurisdictions to a WDI that will be in compliance with US food safety guidelines[8]; however, obtaining updated data for foreign jurisdictions is an ongoing challenge. Those algorithms are particularly useful and fairly conservative from a food safety perspective when used to estimate WDIs for drugs administered to species (eg, sheep and goats) that are considered minor food-producing species in the United States but are major food-producing species in the foreign jurisdiction where the drug is approved. This is because human consumption of those animals is generally greater in the foreign jurisdiction, and the extent of that consumption is considered in the determination of the withdrawal period.

Estimation of WDIs following contaminant exposure

Use of toxicokinetic data is especially important and, in fact, is the only method available for estimation of WDIs after accidental exposure to a contaminant. Common contaminant exposures include routine accidents in which a pesticide is sprayed in an animal enclosure, fire retardant is sprayed on catfish ponds, or a field is sprayed with an unapproved herbicide and then grazed soon after by livestock. Unique cases include treatment of backyard poultry, dioxin contamination of milk in Europe, exposure of pigs to diesel fuel after flooding caused by Hurricane Floyd in North Carolina, exposure of dairy cows in California to botulism resulting from the bailing of cats in hay, exposure of pigs to pet food contaminated with melamine, exposure of farm animals to chemical spills associated with oil fracking, and exposure of livestock to radionuclides following the Chernobyl and Fukushima Daiichi nuclear incidents. Those incidents and the approaches used to manage those exposures have been discussed in previous reviews.[17,27–30] Those issues are also substantially more complex and may not be amenable to the estimation of appropriate WDIs that would allow exposed animals to enter the human food chain. Finally, FARAD recently developed a strategy for the estimation of appropriate WDIs that allow bulk milk (pooled milk from multiple cows generally from multiple operations) from tankers contaminated with violative drug residues that is unsuitable for human consumption to be repurposed and fed to calves instead of being discarded.[31]

Philosophy and Legal Issues Concerning ELDU and FARAD-Estimated WDIs

It is important to clarify that a FARAD-estimated WDI for a drug or contaminant is exactly what it purports to be, an estimate based on the best available scientific data of the time required after extralabel administration of or exposure to a specific drug or chemical for tissue residues of that drug or chemical to decline to concentrations below the FDA-established tolerance. The WDI is not equivalent to the WDT established following labeled use of FDA-approved drugs. The modus operandi of FARAD is to always be conservative; that is, to use available sound pharmacokinetic data to provide veterinarians with a WDI that covers the worst-case exposure and clearance scenarios for the exposed animal or animals. For example, if use of the half-life multiplier method previously discussed results in an estimated WDI of 10 days, but results of a more complete pharmacokinetic analysis suggest a WDI of 12 days, the FARAD-recommended WDI will be 12 days. When sufficient data are unavailable for estimation of a WDI, FARAD will suggest that the affected animals not be slaughtered for human consumption.

All estimated WDIs must balance concerns regarding legal drug use and food safety for human consumers as well as rational treatment to optimize the welfare of the diseased animal while minimizing the economic impact for the producer. In some cases, the recommended WDI following ELDU of a particular drug may be so long that it is not economically feasible for the producer to treat and maintain the diseased animal, and that animal might have to be diverted from the human food chain. Moreover, all FARAD-recommended WDIs are for 1-time exposure

to a contaminant or for extralabel use of a drug for effective treatment or to enhance animal welfare. For example, the labeled doses of some older antimicrobials (eg, penicillins) are no longer effective against today's bacterial pathogens, and use of the labeled dose only serves to promote antimicrobial resistance. Therefore, those antimicrobials must be administered in an extralabel manner and an extended WDI must be observed for treated animals.

Despite AMDUCA, ELDU can be confusing for veterinarians. Certain drugs are prohibited from use in food-producing animals, and FARAD will not provide a WDI for those drugs. The list of drugs currently prohibited from use in food-producing animals in the United States is available on the FARAD website.[32] For some FDA-approved drugs, WDTs are not provided for certain production classes (eg, veal calves or lactating cows) of labeled species because the drug sponsor did not provide the data necessary to establish a WDT for that class of animal. When considering ELDU for a particular animal, it is crucial that veterinarians consider not only the WDI for the drug to be administered but also the intended purpose of the animal in question and proximity of products from that animal entering the human food chain. For example, ELDU might be acceptable for a calf intended for beef production that is not scheduled to be slaughtered for several months but not acceptable for a calf that is intended for veal production and scheduled to be slaughtered within days or weeks. Further information regarding the use of drugs in calves is available in another FARAD Digest.[33] Also, some drugs might be acceptable for use in chickens being raised as broilers (intended for meat production) but not in chickens being raised as layers (intended for egg production). In some cases, animals are accidentally exposed to a drug as a result of a feed mill error instead of administration by or on the order of a veterinarian, and an estimated WDI is required for that specific situation. Finally, ELDU is prohibited for drugs administered in feed to major (eg, cattle, pigs, chickens, and turkeys) and minor (eg, goats and sheep) food-producing species; however, for minor species, a compliance policy guide exists that leaves regulatory action up to the discretion of the inspector. With the veterinary feed directive going into effect in January 2017, this system for providing some flexibility for minor species will need to be reviewed.

To be in compliance with AMDUCA, ELDU requires a valid veterinary-client-patient relationship and is limited to a specific scenario. When FARAD believes a consensus has been achieved, we publish our recommendations in FARAD Digests in the *JAVMA*. However, our recommended WDIs are dynamic and may change as new data becomes available or tolerances and regulations change, and FARAD actively updates published Digests online,[34] something that is not possible with static print publications. Because of the dynamic nature and complexity of determining WDIs, FARAD has always been resistant to publishing hard-copy blanket lists of estimated WDIs.

FARAD Outreach

The primary mechanism for FARAD outreach is via its website.[1] This website is the portal through which estimated WDIs for various drugs can be requested and approved WDTs for all drugs approved for use by the FDA in food-producing species in the United States can be accessed through the VetGRAM database. In its current configuration, VetGRAM allows users to conduct individualized searches on the basis of multiple search variables including a product's trade name or active ingredient, species use or production class, route of administration, drug classification, or new animal drug approval (NADA) number. Information within the resulting search engine report table can be sorted and organized according to species, active ingredient, route of administration, or other user-selected variables. Additional links provide immediate access to additional information about all listed products, including available formulations, approved species, approved indications for use, dosing instructions, warnings or restrictions, and approved regulatory tolerances for the drug or marker residues in different food products. Because regulatory WDTs are predicated on specific conditions of drug use (eg, dose, duration, and route), it is vital that all relevant information be provided to users. The information within VetGRAM is constantly updated and is also available as Apple iPhone and Android smart phone apps. Additionally, FARAD maintains contact with veterinarians via both Facebook and Twitter.

The primary publication outlet is the FARAD Digest feature in the *JAVMA*, of which 25 have been published to date.[13,16,27,30,33,35–54] Originally, those Digests did not undergo peer review because they were simply a vehicle to explain to veterinarians the rationale behind FARAD's estimation of WDIs and a mechanism to communicate general principles of residue avoidance. Current publication policies of *JAVMA* now require Digests to undergo peer review, which has resulted in clarification of some topics. All published FARAD Digests are available through the FARAD website[34] where they are updated as necessary. In addition, FARAD has published pharmacokinetic data compilations in handbook form[2–5] as well as numerous research publications derived from original work, some of which have been previously cited in this Digest. Scientists associated with FARAD frequently attend regional, national, and international meetings to provide information on drug residue avoidance and present our approach and the most current methods that are being used to estimate safe WDIs.

People can contact FARAD by use of a toll-free telephone number.[a] Calls to that number are answered on an alternating basis by professionals at the University of California-Davis, Kansas State University, and North Carolina State University. In fact, answering telephone queries to the FARAD has been part of the training for many veterinary clinical pharmacology residents. Historically, telephone queries were the primary mechanism by which veterinarians could acquire spe-

cific advice on drug or chemical residues; however, the current preferred mechanism is the FARAD online request system[55] because it allows collection of veterinarian contact information and specifics of the case being treated. Online queries are answered by the FARAD responders on call, and challenging cases are assessed by all FARAD regions for scientific input. Internal FARAD databases are also maintained, which provide responders with previous recommendations, useful tools, and access to other data sources.

The FARAD website[1] also provides a number of additional useful tools and links for management of drug and chemical residues including the following:

- A complete list of scientific literature screened by FARAD as useful sources of information regarding drug and chemical depletion.
- A calculator for determining the calendar date when a WDT or WDI is complete.
- Formula for calculations and conversions for drugs, forage, feed, and water consumption.
- A number of educational presentations on drug use in food animals including new reviews focused on specific production classes.
- A full and updated list of regulations that affect drug use in food-producing animals.
- Species pages that provide practical information regarding on-label and ELDU.

Future FARAD Directions

The FARAD has grown primarily in response to pressure from 2 sources, residue issues encountered while responding to queries and scientific progress, primarily in the areas of analytical chemistry, pharmacometric modeling approaches, and information technology. As analytical detection methods for residues improve and tissue tolerances are lowered, recommendations often have to be amended, and the data reanalyzed taking into consideration either new endpoints or data. However, some information technology advances do not immediately advance the program, but rather are changes in software dictated by constantly evolving computer operating systems. We have learned that substantial energy is required to remain stationary and even more is necessary to move forward and ensure that our recommendations are based on current scientific data and assessment.

Since the inception of FARAD, we have made a constant effort to automate as much of the process as possible, creating databases that easily link separate elements. With the rapid advancements in data analytics and raw computing power, this will continue to move forward. At some point, we envision that requests will be automatically processed and WDIs selected by use of a computer by committee or ensemble estimates, where independent simulations are conducted and all results presented, much like the multiple hurricane plots used to predict storm tracks. In the case of residues, the situation is simpler because we are trying to estimate a single point (the tolerance), and the goal is not consensus but rather the worst-case scenario (ie, the longest WDI to ensure food safety given the uncertain data).

Currently, FARAD is in the process of developing a system that will allow us to assess field samples to validate our estimated WDIs. In the past, we have done this by conducting research studies on our own. This area of validation and confirmation will continue to be pursued.

The final area we are trying to develop is essentially a VetGRAM for global drug approvals (ie, the global FARAD program). There are 2 primary motivations for pursuing this endeavor. The first, as mentioned earlier, is to use foreign drug approvals as the basis for calculating a WDI for ELDU in the United States. In many instances, drug use patterns in a foreign jurisdiction may match, or be consistent with, a minor drug use scenario in the United States. The comparison must then take into account the product, formulation, route of administration, dosage, and MRL relative to the US tolerance. The second motivation is to offer guidance to US producers, who export livestock products to foreign regulatory jurisdictions. It is possible that drugs approved by the FDA for use in food-producing species in the United States may have WDTs that are appropriate for avoiding violative residues given the US tolerance but not the MRL or lower analytical detection limit for the foreign regulatory jurisdiction (eg, US tolerance > MRL or lower analytical detection limit). Such data are not currently available in a digital or easily accessible and updated format that allows direct comparisons and analyses to be made.

In conclusion, FARAD is designed to provide veterinarians an information resource regarding the effective use of veterinary drugs in food-producing animals in a manner that will not result in violative drug residues in animal products that enter the human food chain. Many drug approvals (and thus the drug label) are static despite the fact that the WDT was determined on the basis of drug metabolism and elimination in healthy animals and subsequent data indicate that disease may impair drug disposition and elimination in treated animals. Thus, veterinarians may need to recommend extended withdrawal periods for drugs administered to diseased animals, even when those drugs are administered in accordance with the label. Also, the sensitivity of target organisms to specific antimicrobials continuously changes; therefore, veterinarians may have to resort to ELDU of some antimicrobials for effective treatment, which will require an extended WDI. Similar scenarios exist for drug use in minor species, contaminant exposures, or US producers who export livestock products to foreign regulatory jurisdictions. These scenarios are unlikely to change in the foreseeable future, and FARAD will continue to strive to improve its precision in estimating WDIs and provide timely responses to veterinarians' requests for information.

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Footnotes

a. FARAD Hotline, 1-888-USFARAD (1-888-873-2723).

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