

FOOD ANIMAL RESIDUE AVOIDANCE DATABANK (FARAD)



BASICS

OVERVIEW

- The Food Animal Residue Avoidance Databank (FARAD) is a drug and chemical database that can be accessed by veterinarians to obtain drug residue information.
- The ultimate aim of this USDA-sponsored program is to utilize relevant regulatory and pharmacokinetic data to provide farmers and veterinarians with food safety information so that drug and chemical residues are minimized in meat and milk products, thereby reducing public exposure to contaminated food.
- Information regarding the following topics listed below can be obtained from FARAD via the internet website or telephone/e-mail consultation:
 - i. Approved food animal drugs and their approved dose, route(s) of administration, and indications
 - ii. Approved withdrawal times
 - iii. Approved tolerances and foreign maximum residue limits (MRLs)
 - iv. Drug tests
 - v. Management of extralabel drug use in food animals within the guidance of the Animal Medicinal Drug Use and Clarification Act (AMDUCA).

DEFINITIONS

- A US approved meat and milk **withdrawal time** is the time it takes for a drug to reach the approved tolerance level. The withdrawal time is determined by the pharmaceutical company after performing a series of pharmacokinetic studies and analysis of the data prior to submission to the US FDA for approval. The most critical pharmacokinetic parameter used in the determination of the drug withdrawal time is the milk or tissue half-life of the drug in the stated animal species.
- The **half-life** is the time required for the amount of drug in tissues to decline by 50%, and it is often independent of drug dose.
- The **tolerance** or **maximum residue limit** (MRL) is the regulatory drug concentration above which there may be adverse health effects if humans were to consume animal derived food containing drugs above the tolerance or MRL. The United States uses the term tolerance while other countries and international organizations use the term MRL. If the FDA deems that the tolerance needs to be adjusted, this could either increase or decrease the withdrawal time.
- A **residue** means any compound present in edible tissues that results from the use of a drug, and includes the drug, its metabolites, and any other substance formed in or on food because of the drug's use.
- The United States Department of Agriculture Food Safety Inspection Service (USDA FSIS) inspects food for the presence of drug and other chemical residues.
- Potential sources of residues in animal-derived food include:
 - i. Not following the approved label
 - ii. Not using the approved labeled withdrawal time
 - iii. Physiological/clinical scenarios that may prolong clearance of the drug from the animal's body.

RELEVANT US FEDERAL LAWS

- The *Animal Medicinal Drug Use and Clarification Act (AMDUCA)* in 1994 allowed for the extra-label use of veterinary and human drugs in food animals. This law is not to be interpreted as federal promotion of extra-label drug use, and there are several Extra-label Drug Use (ELDU) Guidelines which the veterinarian is encouraged to follow when considering extra-label drug use in food animals. They include:
 - i. Establishing a valid veterinarian-client-patient relationship
 - ii. There exist no currently marketed drugs for the disease or the recommended dose is ineffective
 - iii. Maintain records and other measures to identify the treated animals
 - iv. Significantly extending the approved withdrawal time to ensure that there are no possibilities of illegal drug residues in meat or milk products.
- There is also a growing number of drugs that are prohibited for extralabel use in livestock destined for human consumption. As of October 2015, they include
 - Chloramphenicol
 - Clenbuterol
 - Colloidal Silver
 - Diethylstilbestrol (DES)
 - Dipyrone
 - Nitrofurazone/Furazolidine
 - Nitroimidazoles
 - Glycopeptides
 - Phenylbutazone is prohibited from extralabel use in female dairy cows greater than 20 months old
- The following drugs are also prohibited from extralabel use in food producing species
 - Fluoroquinolones
 - Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine)
 - Cephalosporins (not including cephalixin) in cattle, swine, chickens, or turkeys for disease prevention purposes at unapproved doses, frequencies, durations, or routes of administration or if the drug is not approved for that species and production class
- In dairy cattle, the use of two drugs that are not currently on the AMDUCA extralabel prohibited list but which are not allowed by the pasteurized milk ordinance include non-medical grade dimethyl sulfoxide (DMSO) and colloidal silver. Medical-grade DMSO may be prescribed by a veterinarian in an extra-label manner to treat life threatening conditions in dairy cattle, but industrial grade use in dairy cattle is prohibited.
- Any feed additive intended to be fed to major livestock species such as cattle, swine, or poultry is also prohibited from extra label use. The prohibition of using feed additives in an extra-label manner does not apply to minor species such as goats and sheep, but there must be a valid veterinarian-client-patient relationship.
- Veterinarians are strongly discouraged from extra-label use of aminoglycosides in food animals because these drugs can persist in renal tissue for as long as 18 months.
- On April 11, 2012, FDA finalized a guidance document entitled “The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals” (Judicious Use Guidance, GFI #209). Based on the available scientific evidence concerning antimicrobial resistance, including information about resistance trends associated with the use of medically important antimicrobial drugs in food-producing animals, the FDA believes that the judicious use of medically important antimicrobial drugs intended for use in food-producing animals should involve the clinical training of a licensed veterinarian. This is because judicious use involves accurately identifying bacterial disease that is present or likely to be present and selecting the suitable antimicrobial drug. Guidance for Industry #213 defines appropriate therapeutic uses of antibiotics in food animals as the “treatment, control, and

prevention of specific diseases necessary for assuring the health of food-producing animals.” The FDA would not consider the administration of a drug to apparently healthy animals in the absence of any information that such animals were at risk of a specific disease to be judicious, which includes growth promotion claims. These guidance rules will go into effect by the end of December 2016.

RULE-OF-THUMB APPROACH FOR ESTIMATING WITHDRAWAL PERIODS

- By significantly increasing the dose, a veterinarian in the field can use the following general rule-of-thumb as an initial recommendation to the producer and then refining this estimate after consulting with FARAD or drug company: By assuming that it takes three half-lives for the body to remove most of the drug, the veterinarian can divide the approved withdrawal time by 3 to obtain what FARAD considers as the “apparent” half-life for the target tissue that will be tested by US FSIS. This allows the veterinarian to add half-lives as the dose is increased.
- For example, if the approved withdrawal time is 30 days, the apparent half-life is 10 days (30 days/3) and the veterinarian can extend the withdrawal period from 30 days to 40 days if the dose was doubled or to 50 days if the approved dose was quadrupled. This is a very conservative approximation of the tissue half-life as the real tissue half-life is considerably shorter, but this approach provides the veterinarian with a scientifically-based estimation. Simply doubling the withdrawal time for a doubled dose is not scientifically-based and provides an unnecessarily long withholding time. The use of half-life multiplication to estimate extended withdrawal intervals in food producing species as explored in a publication by Gehring et al. (2004).
- By administering a drug to a species different from that for which the drug is approved, the veterinarian can make an estimation based on known metabolic or clearance mechanisms for a similar class of drugs. For example, small ruminants can in most cases more readily metabolize drugs than cattle and clearance will therefore likely be greater in the small ruminant. In situations where there is limited data within FARAD for the species in question, FARAD will extend the approved withdrawal time in cattle by 24-48 hours for a drug given to small ruminants. Although clearance may be greater in the small ruminant than cattle for that class of drugs and thus should have a shorter withdrawal period, the AMDUCA strongly recommends that in ANY extra-label drug use scenario, the extra-label withdrawal period must be extended; that is, it is illegal to shorten the withdrawal period. Age of the animal is another consideration, since a wide variety of age relevant factors alter clearance values. The effect of age (ruminant calves vs. non-ruminating calves) on drug disposition was again recently demonstrated in a scientific study (Mzyk et al., 2016), which needs to be considered when extrapolating adult data to neonatal animals.
- By administering a drug via a route different to the approved route, it is difficult to estimate a safe withdrawal period unless the veterinarian consults with FARAD or the drug company. For example, even though Cydectin® (moxidectin) may be labeled for topical use in cattle with a zero meat and milk withdrawal time, it does not necessarily mean that the meat withdrawal time will be zero if this product is given orally. Penicillin G Procaine is an example of a commonly used approved animal drug that requires significant changes in withdrawal interval recommendations based on dose, route and species as well as changes in sensitivity of regulatory testing (DeDonder et al, 2013). The effects of route on clearance of drugs in cattle has been demonstrated (Lindsey et al., 2012). The influence of disease on the clearance of drugs ruminants has also been recently examined, (Kissell et al., 2015; Smith, et al., 2015), and veterinarians should be aware that some clinical scenarios could influence the meat and/or milk withholding time for some drugs.

FARAD CONTACT INFORMATION

- In each of the above extra-label drug use scenarios described above, the veterinarian is encouraged to consult FARAD to obtain a better estimate of an extended withdrawal period. FARAD can be contacted via web submission at www.farad.org or can be reached by telephone (1-888-USFARAD).
- Finally, the veterinarian should also inform the producer that these estimates are not Federally approved withdrawal times and therefore are subject to change as more information becomes available to FARAD. Because of this and the fact that each extra-label scenario can be case-specific, FARAD does

not routinely publish lists of extra-label withdrawal periods. However, FARAD will occasionally publish extra-label withdrawal period information in Digest Articles in the Journal of the American Veterinary Medical Association (JAVMA) for a drug class or minor species only when there is sufficient information in the database that improves confidence in these estimates.



MISCELLANEOUS

SEE ALSO

- Controlled Substances (www.fiveminutevet.com/ruminant)
- Drug Hypersensitivities
- Drug Toxicities
- Drug Storage Requirements and Veterinarian-Client-Patient Relationship (VCPR) (www.fiveminutevet.com/ruminant)
- Extra-label Drug Use and Compounding (www.fiveminutevet.com/ruminant)
- Nonsteroidal Anti-inflammatory Drugs (NSAIDs) (www.fiveminutevet.com/ruminant)
- Common Pharmacologic Therapies: Adult dairy cattle (www.fiveminutevet.com/ruminant)
- Pharmaceutical Use: Legal Issues (www.fiveminutevet.com/ruminant)
- Pharmacokinetics and Pharmacodynamics (www.fiveminutevet.com/ruminant)
- Medical Waste Management: Expired Drugs (Appendix 3)

ABBREVIATIONS

- AVMA = American Veterinary Medical Association
- AMDUCA = Animal Medicinal Drug Use Clarification Act
- DES = diethylstilbestrol
- DMSO = dimethyl sulfoxide
- ELDU = Extra-label drug use
- FARAD = Food Animal Residue Avoidance Databank
- MRLs = Maximum residue limits
- U.S. FDA = United States Food and Drug Administration
- USDA FSIS = United States Food Safety Inspection Service
- USDA = United States Department of Agriculture

Suggested Reading

http://wildpro.twycrosszoo.org/S/00Man/PainRumOverviews/PainGeneral/03Pharmacokinetics_PainRum.htm

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