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THE FARAD NEWSLETTER

An electronic publication from the Food Animal Residue Avoidance Databank (FARAD) for veterinarians, animal scientists, extension specialists and the regulatory community.

**March 5, 2003
Issue # 3
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1. FROM THE EDITOR

It has been a busy first quarter in terms of food animal residue news. There have been several new food animal product approvals, phenylbutazone has been added to CVM's "prohibited" list and FSIS has started posting the names and addresses of repeat violators on the Internet. Of particular importance to us at FARAD is the opening of a Canadian FARAD office. Funded collaboratively by the Canadian government and industry sources, this center will offer the same services to Canadian veterinarians and producers that US FARAD provides in the States. US FARAD has been funded for yet another year and we are grateful for the support that many of you have provided. Still, keeping technically competent staff is difficult with only a year-to-year promise of funding and we are directing efforts towards inclusion of FARAD as a "line-item" put forth in the federal budget every year. Such a funding mechanism would offer greatly increased stability to our program and would minimize service disruptions like those that have occurred in the past. In the flurry of work surrounding the omnibus federal budget bill this year, for instance FARAD was very nearly overlooked. We will keep you apprised of any progress.

Michael Payne DVM, PhD
University of California, Davis

2. CANADIAN FARAD OFFICE OPENS

The FARAD concept was established in 1982 as a cooperative project between four US veterinary colleges and the US Department of Agriculture's Food Safety and Inspection Service as a way to reduce the rate of residue violations in animal products through education and information. The founding philosophy of FARAD was that information about residue avoidance from all sources should be immediately available from a scientific source. The FARAD was developed to not only contain information related to approved animal drugs but to also include information on extralabel drug use and environmental toxins. For this "one-stop shopping" information service to work, the FARAD information was collated into a searchable computer database, with residue and pharmacokinetic data analyzed and interpreted by veterinary pharmacologists and toxicologists. Currently, the FARAD database includes over 1200 drugs and chemicals and over 20,000 pharmacokinetic records extracted from over 9000 citations. For 20 years, the US FARAD centers have been providing accurate and timely information to veterinarians to protect the US food supply.

Although not widely known in the US, FARAD is a part of a global FARAD (gFARAD) international collaboration. In addition to the three US FARAD centers, foreign university/government collaborations have funded the establishment of centers in France, Spain and the United Kingdom. Global FARAD also has a formal partnership agreement with the United Nations's Food and Agriculture Organization.

Each member country is responsible for establishing their own permanent national access centers. With a yearly subscription to gFARAD, each member country receives web-based access to the FARAD database along with customized software and technical training from the original US centers. In return, gFARAD members collect, standardize, and enter into the global database all relevant drug and chemical information and tolerance data from their countries. This global partnership provides a single web-accessible compendium of drug information and tolerance data, to which only member countries have access. This pooling of data greatly augments efforts to ensure that withdrawal recommendations and interspecies extrapolations are based on the best scientific information available. The gFARAD system will also aid in the harmonization of acceptable international standards for veterinary drug use.

The newest addition to the international FARAD family is Canadian gFARAD. Canadian gFARAD is comprised of two centers located at the Western College of Veterinary Medicine in Saskatoon, SK and the Faculté de médecine vétérinaire at St Hyacinthe, QC. Free bilingual service started last October 1 and is available at 1-866-C-GFARAD (1-866-243-2723). Canadian gFARAD's website www.cgfarad.usask.ca, also contains information for submission of questions by FAX or email. Routine inquiries are typically answered within one working day (eastern time zone), while complex residue problems may require a longer period of time. During non-working hours, messages can be left 24 hours a day. The Canadian gFARAD centers will provide expert-mediated decision support for any inquiry related to drug or chemical residues in food animals. Canadian gFARAD personnel will assist veterinarians or government agencies with inquiries related to environmental contamination or bioterrorism. Extralabel drug withdrawal information will only be provided to veterinarians authorized to practice in Canada because of their privilege and responsibility in using or prescribing drugs in an extralabel manner.

Canadian gFARAD website:
www.cgfarad.usask.ca

General Information on Global FARAD is available at:
www.gfarad.org/

Press release on Canadian FARAD is available at:
www.cahi-icsa.ca/english/publications_inforum_v6no3.pdf

Lay press article on Canadian FARAD is available at:

www.producer.com/articles/20020919/livestock/20020919ls02.html

3. NEW FLUROQUINOLONE APPROVED IN BEEF CATTLE

Pfizer has received approval to market its new fluoroquinolone product "A180". The drug is labeled for the treatment of bovine respiratory disease (BRD) associated with *Pasteurella haemolytica* and *Pasteurella multocida*. Each milliliter of solution contains 180 mg danofloxacin mesylate. The label dose is 6 mg/kg body weight given by subcutaneous injection to be repeated 48 hours later. Extralabel use of fluoroquinolones in food animals is illegal. This product may only be used exactly according to label. This product may not be used in any food animal species other than cattle. This product may not be used in dairy cattle nor in cattle intended for dairy production. This product may not be used in veal calves. Label withdrawal time for slaughter is 4 days. The tolerance for parent danofloxacin (residue marker) was established at 0.2 ppm in liver (target tissue) and muscle.

The Pfizer Animal Health home page is:

www.pfizer.com/ah/

The Freedom of Information summary for the product is available at:

www.fda.gov/cvm/efoi/section2/141-207.pdf

General Information on Prohibition of Fluoroquinolones in Food Animals

www.fda.gov/cvm/index/fdavet/2002/NovDec.htm#Fluorquinolones

4. PHENYLBUTAZONE ADDED TO PROHIBITED LIST

Effective May 29, 2003 the Food and Drug Administration (FDA) will prohibit extralabel use of phenylbutazone animal and human drugs in female dairy cattle 20 months of age or older. The FDA is issuing the order based on evidence that extralabel use of phenylbutazone in female dairy cattle 20 months of age or older will likely cause an adverse event in humans. With this action the use of any phenylbutazone in an adult dairy cow becomes a violation of the Food Drug and Cosmetic Act and one of FDA's highest regulatory priorities. The FDA invites written or electronic comments on the order until April 29, 2003.

With the May 29, 2003 implementation of this order, the list of drugs prohibited from extralabel use in food animals (in chronological order of prohibition) will be:

Diethylstilbestrol (DES)

Chloramphenicol

Nitroimidazoles (including dimetridazole, metronidazole and ipronidazole)

Sulfonamide use in adult dairy cattle*

Clenbuterol

Dipyron**

The fluoroquinolones (examples enrofloxacin and danofloxacin)

The glycopeptides (example vancomycin)

Nitrofurans (including nitrofurazone, furazolidone, topical use prohibited as well)

Phenylbutazone use in adult dairy cattle*

*Lactating (adult) dairy cattle are defined by FDA as dairy cattle 20 months of age or older regardless of whether they are milking or dry. Currently the only sulfonamide available for use in dairy cattle older than 20 months of age is sulfadimethoxine (SDM). In adult dairy cattle this drug may only be used on-label. Administering higher doses or sustained release SDM products is prohibited. Aside from the above AMDUCA list, regulations related to the Pasteurized Milk Ordinance (PMO) prohibit the presence of dimethyl sulfoxide (DMSO) and colloidal silver on dairies. In addition, the use of ionophore compounds (i.e. monensin, lasalocid) in lactating dairy cattle rations is prohibited.

** Because dipyron-containing products are not available for either humans or animals, it is not typically included on lists of extralabel prohibitions published by CVM. Old stockpiles of the drug, however, do

occasionally surface. Any use of dipyrone in food animals remains a violation of the Food Drug and Cosmetic Act.

The entire text of the order of prohibition can be viewed at:

www.fda.gov/OHRMS/DOCKETS/98fr/03-4741.htm

5. TILMICOSIN APPROVED IN SHEEP

Elanco Animal Health has received approval to market its tilmicosin product "Micotil 300 Injection" in sheep. The drug is labeled for the treatment of ovine respiratory disease (ORD) associated with *Pasteurella haemolytica*. Each milliliter of solution contains 300 mg tilmicosin phosphate. The label dose is 10 mg/kg body weight given by subcutaneous injection. Label withdrawal time for slaughter is 28 days. The tolerances in sheep are the same as in cattle: tolerance for parent tilmicosin (the marker residue) in liver (the target tissue) is 1.2 ppm and tolerance in muscle is 0.1 ppm.

The approval of tilmicosin in sheep was accomplished in part through the National Research Support Project #7 (NRSP-7), the Minor Use Animal Drug Program. This cooperative university, federal and pharmaceutical industry program's mission is approval of animal health products for minor uses and species. The program provides financial support for efficacy, animal safety, food safety and environmental impact studies necessary for approval in species whose market would normally be insufficient to justify costly research expenditures by the private sector. For example, of the eight drugs approved for use in goats in the US, five (morantel tartrate, fenbendazole, decoquinate, monensin and ceftiofur) were approved through NRSP-7. Only three (neomycin, proparacaine and thiabendazole) were approved through the normal regulatory approval process.

The Elanco Animal Health home page is:

www.elanco.com/

The Freedom of Information summary for the product is available at:

www.fda.gov/cvm/efoi/section2/140-929.pdf

The NRSP-7 (the Minor Use Animal Drug Program) home page is: www.nrsp-7.org and their on-line drug database MUMSRx is available to the public there. FARAD has a formal data sharing arrangement with NRSP-7 and is supplying the data for the MUMSRx database of drugs approved for minor species and minor uses.

6. FLORFENICOL APPROVED FOR SWINE IN DRINKING WATER

Schering-Plough Animal Health has received approval to market its new florfenicol product "Nuflor 2.3% Concentrate Solution" to be used to make medicated drinking water the treatment of respiratory disease in swine associated with *Actinobacillus pleuropneumoniae*, *Pasteurella multocida*, *Salmonella choleraesuis* and *Streptococcus suis* Type 2. The label dose is 400 mg per gallon (100 ppm) provided in the drinking water over 5 consecutive days. Label withdrawal time for slaughter is 16 days. A tolerance of 2.5 ppm for the marker residue florfenicol amine was established in swine liver (the target organ) and 0.2 ppm in muscle.

The Schering-Plough Animal Health home page is:

<http://usa.spah.com/home.cfm>

The Freedom of Information summary for the product is available at:

www.fda.gov/cvm/efoi/section2/141-206.pdf

7. FSIS POSTS RESIDUE VIOLATIONS ON INTERNET

On January 6, 2003, FSIS began its online Residue Information Center which provides the names and addresses "of the persons responsible for the repeated sale of livestock or poultry that contain chemical residues above the established tolerance levels". Any producer with more than one citation for misuse of animal drugs within a twelve-month period will be considered a "repeat violator." Relative to the on-line list, FSIS started all producers off with a clean-slate, so that the only names currently on the list are of those

who have had at least two violations since the program began. The FSIS Federal Register notice, which contains public comments on the Center, has been published in the Federal Register.

Residue Information Center:

www.fsis.usda.gov/OPPDE/ric/

Federal Register Notice on the Center:

www.fsis.usda.gov/OPPDE/rdad/FRPubs/02-014N.htm

8. FDA REVISES DEFINITION OF TERM “NO RESIDUE”

FDA has published a final rule that revises the definition of “no residue” in the new animal drug regulations to mean that no residue is detected with an approved regulatory method. This means that any residue in the target tissue must be non-detectable or below the limit of detection (LOD) of the approved regulatory method. This rule clarifies the term “no residue” in another regulation which implemented the “DES proviso” of the Delaney Clause to the Federal Food, Drug, and Cosmetic Act. This provision permits the approval of a new animal drug which induces cancer if “no residue” will be found, by methods prescribed or approved by the Secretary, in edible tissues of treated animals.

The entire text of the rule can be viewed in the Federal Register:

www.fda.gov/OHRMS/DOCKETS/98fr/02-32216.htm

9. EXTRALABEL USE OF MEDICATED FEEDS FOR MINOR SPECIES

AMDUCA’s Section 530.11 specifically prohibits the “extralabel use of an approved new animal drug or human drug in or on an animal feed”. As a matter of enforcement discretion, CVM generally has not objected to mixing a drug with an individual animal’s feed, but extralabel mass medication in feed was prohibited “without limitation or exception”. FDA has determined that for some minor food animal species (game birds, fish) for which there are very few approved drugs, the only practical method of delivery is in the feed. CVM/FDA has adapted a new Compliance Policy Guide (CPG) Sec. 615.115 (“Extra-label Use of Medicated Feeds for Minor Species”) which addresses that need. This CPG applies only to minor food animal species, which by definition is any food animal which is not a cow, pig, chicken or turkey.

There are several notable caveats. Most importantly this CPG does NOT make the practice of extralabel drug administration in feed legal. While AMDUCA made most extralabel administrations legal, the extralabel use of drugs in feed however is still a violation of the federal FD&C Act. What this CPG does is more akin to the situation prior to AMDUCA, where the practice was illegal but FDA would “not ordinarily will not consider regulatory action” if certain conditions were met. These conditions make it clear that the policy does not give the veterinarian carte blanche and are in fact quite onerous. For instance only medicated feeds already formulated, manufactured and labeled for a major species may be used. In addition the use of medicated feed in aquaculture is limited to medicated feed products approved for use in aquatic species. The use of medicated feed is limited only to farmed or confined minor species. All the usual record keeping and extended withdrawal requirements apply. A VCPR must exist. As was true both pre-AMDUCA and now, if a residue occurs, any liability would rest with the practitioner and producer. A veterinarian choosing to violate the Food Drug and Cosmetic Act under this policy should carefully review the CPG and consider the amount of liability he or she is willing to accept.

The entire text of the Compliance Policy Guide can be viewed at:

http://www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg615-115.html

10. EXTRALABEL TREATMENT OF EXPERIMENTAL FOOD ANIMALS

FARAD has received a number of inquiries regarding what type of drug use is permitted in experimental animals. What follows is a bullet point summary of drug use in experimental food animals.

A. A researcher (like a practitioner) may administer to a food animal any drug he or she can legally obtain and administer under AMDUCA and subsequently market the animals. This includes pain relievers, anesthetics, antibiotics etc. Both practitioners and researchers administering extralabel treatment to food animals to be marketed must prescribe an extended withdrawal time based on adequate scientific data. If

adequate scientific data does not exist then the researcher/practitioner must insure that the treated animal does not enter the human food chain.

B. AMDUCA does not allow practitioners or researchers to use extralabel drug administration for production purposes (oxytocin for milk production, hormones to regulate reproductive cycles).

C. A researcher can give an unapproved, experimental drug to food animals that DO NOT enter the food chain. Researchers doing so are obligated to fulfill record-keeping requirements outlined under 21 CFR 511.1(a) .

D. A researcher can give an unapproved experimental drug to and market food animals ONLY if he or she has obtained an Investigational New Animal Drug (INAD) permit (with slaughter authorization) through the Food and Drug Administration's Center for Veterinary Medicine.

E. None of these federal obligations address requirements that an individual research institution might have, such as protocol review by an Animal Care and Use Committee.

11. VetGRAM

Most of you are aware that VetGRAM [veterinarian's Guide to Residue Avoidance Management], FARAD's on-line database of FDA approved food animal drugs has been totally revised and is now available on the web site in the "veterinarian" section. We are working on setting up a user-friendly password system [you set and change your own password and can retrieve it if you lose/forget it]. We anticipate that it will be available within the next couple of weeks so keep tuned. In the meantime you can use the introductory username of <CPTCNT\PrevieW> and the password <.fArAd>. Please watch both case and punctuation (there is a period at the start of the password). If you have any problems getting through or have problems/comments with VetGRAM itself please contact FARAD at the University of Florida (farad@mail.vetmed.ufl.edu).

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