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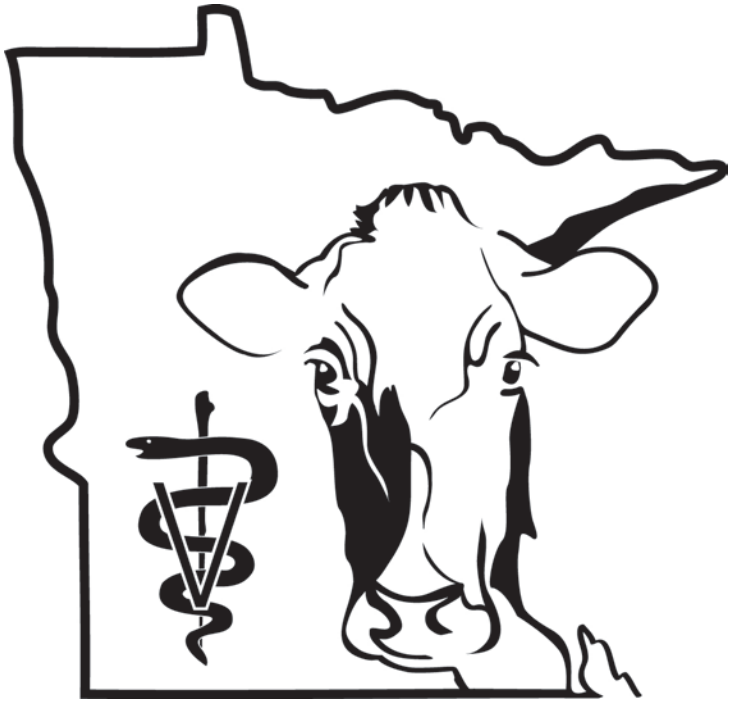

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Updates from FARAD and the Minor Species Drug Approval Program

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The Current Regulatory Environment

Recent years have seen state and federal regulatory agencies focusing increased attention on the issue drug residues in food animals. The Food and Drug Administration (FDA) has begun investigations into the large-scale use of gentamicin by calf raisers. The agency has also increased slaughter plant surveillance for analgesic residues, particularly phenylbutazone and flunixin. Several states have begun using highly sophisticated racehorse testing technologies to analyze urine from fair animals.

When a particular producer is identified as a chronic violator, FDA has increasingly used the tool of court-ordered injunction. Typically in these situations the producer is brought before a federal district court judge who injoins him from selling animals until a variety of management remedies are in place. Producers failing to implement court's corrections face fines, closure and, in the case of one California dairyman, a jail sentence.

In the near future producers will feel pressure not only from regulatory agencies but from packinghouses as well. Under USDA's HACCP-based inspection program, when a residue is detected a notice of violation goes not only to the producer but to the slaughter facility as well. Faced with a court-ordered plant closure, some packers are giving notice to sale barns that they will not accept cull cows from specific producers. The USDA is working on making dairies' residue histories freely available on the Internet, which will assist packers in applying this market-place pressure.

As producer liability increases so does the veterinary practitioner's. There are two state/ federal cooperative programs that provide assistance to veterinarians seeking to avoid problems with drug residues.

NRSP-7, the Minor Species Drug Approval Program

The shortage of drugs for minor food animal species is a problem well recognized by producers and veterinarians. Minor animal drug uses are analogous to human orphan drug uses, for which the market is insufficient to justify the costly research expenditures by pharmaceutical firms. In 1982 the USDA and FDA collaborated to established a program whose purpose is facilitate drug approval for minor food animal species. Minor species is defined as any food animal species except for cattle, swine, chickens and turkeys. The resulting National Research Support Project No. 7 (NRSP-7) makes federal funds available for the efficacy, animal safety, human food safety and environmental assessments required for drug approval.

Research projects are typically initiated by requests from researchers or animal producers. These Animal Drug Requests (ADRs) are prioritized by a technical committee according to financial and regulatory feasibility, and importance to the animal industry. ADR request forms are available at the NRSP-7 web site (www.nrsp7.org). Research

projects are most often approved for compounds that already have a major species approval. In addition, it is preferable that the pharmaceutical company holding the major species approval expresses a desire to take the drug to market once the compound evaluation is complete. Research projects are coordinated through one of four collaborating Universities, although frequently portions of a project may be subcontracted to other sites having researchers having expertise or access to a particular species. All work is performed under Good Laboratory Practices (GLP) Guidelines.

Each drug evaluation consists of efficacy studies, target animal safety studies, human food safety studies (residues), and an environmental assessment. Of some 295 ADRs submitted to the program, FDA has accepted completed data packages (called Public Master Files or PMFs) for 27 compounds (Table 1). Of these 27 drugs, 21 have been brought to market with new labels for a minor species. There are an additional 27 active research projects currently being conducted in 15 states involving 18 different species (Table 2). Thus, program funding has been available for only about one in six requests. Never the less the program is remarkably cost efficient. Each PMF costs about $200,000, considerably less then the several million dollars typically required for an animal drug approval achieved through the usual channels.

FARAD, the Food Animal Residue Avoidance Databank

FARAD was created in 1982 as a state/federal cooperative educational outreach program. The fundamental program concept was that information about residue avoidance from all sources should be immediately available from a single access point. The database was to include information not only related to approved animal drugs, but extra-label applications and environmental toxicants as well.

In order for the "one stop shopping" model to have any practical value, the information would have to be collated into a searchable database. In addition, because a simple listing of citations would have little pragmatic application to practitioners, veterinary pharmacologists needed to be available to analyze and interpret the data. This expert-mediated decision support has endured as the most unique and important service offered by FARAD. Program personnel will assist any person (producer, regulator, student, etc.) with an inquiry related to chemical residues in food animals. Extra label withdrawal times, however, are supplied only to veterinarians because of their unique privilege and responsibility in being able to use or prescribe drugs in an extra-label fashion.

While FARAD software and hardware has been continuously upgraded, the model of a relational database allowing for a cross-referenced search by species, animal class, chemical, author, and source title has remained constant. In order to keep pace with evolving science and novel inquiries, the database has grown throughout the years. From the original 119 chemicals and 700 references, the database has grown to include some 1,200 compounds and approximately 26,000 pharmacokinetic records extracted from 4,800 citations. Additional files pertaining to approved food animal drugs, tissue and milk tolerances and available educational materials were also created.

Extra label withdrawal intervals represent only a portion of the information supplied by FARAD. Inquiries are varied and may relate to label indications and withdrawal times, drug labeling and storage, tolerance data or rapid screening test availability. If the requested information does not exist in the database, FARAD's close ties with various state and federal regulatory agencies, animal industry organizations, pharmaceutical companies and other research programs usually result in a satisfactory response. While unusual requests may take a week or more for a response, standard recommendations exist for the most commonly asked questions (Table 3).

For almost 15 years FARAD published *A Comprehensive Compendium of Food Animal Drugs,* which summarized current label information for all food animal drug. In spite of frequent updates, rapid change in drug availability meant that this reference become dated quickly. In order to offer clients more timely data, FARAD is redesigning it's Internet web site (www.farad.org). The web site is to be updated frequently and will provide one of the most current sources of data for producers and veterinarians regarding approved drugs.

In order to meet emerging challenges related to technical and trade issues in food safety, FARAD has become as much a research project as an extension service. Current investigations include inter-species data extrapolation, novel kinetic modeling, disease-altered pharmacokinetics, population pharmacokinetics and the relationship of serum pharmacokinetics to tissue residues.

Another major effort has been the establishment of a multi-national cooperative program called Global FARAD (gFARAD). Cooperating countries receive technical assistance (including customized software and training) in establishing their own FARAD centers. In return these international partners provide relevant drug registration and tolerance data from their countries. The pooling of data will greatly augment efforts to ensure that U.S. extra-label recommendations and inter-species extrapolations are based on the best scientific data available. The collaboration will also aid in the harmonization of acceptable international standards for veterinary drug use. With the assistance of the United Nation's the Food and Agricultural Organization, France has already established gFARAD's first international center. The United Kingdom and Spain have funded centers and Australia and Switzerland are expected to do likewise.

Illustrative FARAD Case Histories

The following case histories have been selected from FARAD's call records to illustrate both the type of information supplied by FARAD and emerging issues for the food animal practitioner.

<u>Dipyrone in Beef Cattle</u>

A Minnesota cattle farmer in possession the analgesic dipyrone asked a local practitioner, whom he employed only infrequently, for a meat withdrawal time. FARAD informed the veterinarian that the drug was "banned" from use in food animals and represented one of FDA's highest regulatory priorities. FARAD frequently fields questions regarding what may be done legally under the auspices of AMDUCA. In the event that an animal

had *already* been treated with dipyrone, FARAD could have provided an appropriate withdrawal interval.

Xylazine in Lactating Goats

A Georgia veterinarian attending several goat herds requested meat and milk withdrawal intervals the sedative xylazine. Published cattle studies indicated no detectable residues in milk or tissues by 24-72 hours following IM treatment. Extension of cattle recommendations to sheep and goats was supported by published pharmacokinetic data that indicated similar half-lives and volumes of distribution in all species studied. In addition, our recommendations were conservative relative to foreign approvals. This case illustrates two of the most frequent mechanisms by which FARAD arrives at its recommendations, review of published literature and the use of foreign drug labels.

Heptachlor in Missouri Dairy Herds

A FDA inspector sampling feed for aflatoxin in Missouri noticed the presence of pink seed kernels indicating pesticide treatment. The treated seed grain had been used to make fuel alcohol and then illegally sold as an inexpensive by-product feed. Milk from more than 80 producers was quarantined, some having milk residues 900 times the FDA's action level. FARAD re-analyzed heptachlor data collected in the 1950's and 1960's using contemporary pharmacokinetic methods to accurately predict how long milk would be discarded. This case portrays another tool at FARAD's disposal, the re-analysis of existing data in order to derive information that previously did not exist.

Phorate TMR Mixing Error on a Dairy

A bag of the highly toxic organo-phosphate insecticide phorate was inadvertently mixed into the TMR of a 600 cow California dairy. Of approximately 200 exposed cows, 167 died, some while eating. Testing revealed no residues in milk at 24 hours and no tissue residues in surviving animals after 5 days. While minimal data was available in the literature for use in this case, the laboratory data collected was useful in answering questions involving a subsequent phorate exposure in a Nebraska beef herd. This case depicts the utility a central clearinghouse of residue information, since knowledge gained from previous cases can be applied to new ones.

Dairy Herd Exposed to Pesticide-Treated Pasture

An Iowa dairy herd grazed an oat field sprayed 8 days earlier with the organo-phosphate insecticide chlorpyrifos. When consulted the pesticide manufacture recommended a two-week milk withdrawal. Based on data supplied by FARAD, the dairy was released from quarantine almost immediately.

Beef Heifers Exposed to Fungicide-Treated Seed Grain

In Montana twelve bred beef heifers (still 5 months from preg-check) gained access to a bin containing 50 pounds of barley seed grain treated with the fungicide difenoconazole. Based on unpublished studies made available from the manufacturer, FARAD recommended a conservative one-month withdrawal time, far less then the next potential culling time.

Mirex in Texas Beef Cattle

Cattle from a 100-cow Texas beef herd "broke into" a shed containing 20-year old bags of the banned fire-ant poison Mirex. Published data suggested a *tissue half-life of between one and ten years*. Mirex is a known animal and suspect human carcinogen. FARAD located a laboratory that could assay fat samples, allowing for the destruction of only those animals that had actually consumed the toxin.

Phenylbutazone in a Show Steer

An Ohio veterinarian administered 4 grams of phenylbutazone horse paste to a show steer for an acutely injured leg. Phenylbutazone and metabolites were detected in a urine sample collected following the show, but not before the slaughtered cow's tissue was mixed with that from a number of others. In all 30,000 pounds of product was destroyed. The issue of reparations has yet to be resolved, but the veterinarian is particularly at risk given the availability of an approved analgesic for beef cattle, flunixin.

Botulism Outbreak on a California Dairy

Some 160 lactating cows died of botulism over a period of more then a week in California. By the time the outbreak was recognized, milk from affected cattle had been used in the making of several million dollars worth of dairy products. Because FARAD's literature search revealed only a single rodent study investigating botulinum toxin transfer into milk, the state's dairy industry has sponsored a $85,000 study examining the question. Identifying data gaps remains an important service performed by FARAD.

Nitrofurazone Puffer use on a Prison Herd

During a pinkeye outbreak in a Ohio prison herd, 34 beef cattle were treated topically with nitrofurazone. Because this product was recently placed on FDA's list of compounds prohibited from use in food animals, the state, USDA and the FDA all became involved. All agencies eventually accepted FARAD's science based recommendation but the case illustrates the extremely high regulatory priority which is placed on prohibited compounds.

Table 1: Completed Public Master Files (PMFs) and resulting new label approvals.

ADR	DRUG	SPECIES	INDICATION	STATUS*
1	Monensin	Goats	Coccidiosis	Approved
111	Decoquinate	Goats	Coccidiosis	Approved
124	Fenbendazole	Goats	GI parasites	Approved
144	Morantel tartrate	Goats	GI parasites	Approved
17	Ivermectin	Goats	GI parasites	PMF
95	Levamisole	Goats	GI parasites	PMF
112	Clorsulon	Goats	Liver flukes	PMF
8	Albendzaole	Goats	Liver flukes	PMF
14	Decoquinate	Sheep	Coccidiosis	Approved
165	Ceftiofur	Sheep	Bacterial pneumonia	Approved
87	Amoxicillin	Sheep	Respiratory disease	PMF
127	Fenbendazole	Sheep (bighorn)	Lungworms	PMF
11	Ivermectin	Reindeer	Warbles	Approved
125	Ivermectin	Bison	Hypodermosis	Approved
110	Ivermectin	Fox	Ear mites	Approved
122	Lasalocid	Rabbits	Coccidiosis	Approved
2	Amprolium	Pheasants	Coccidiosis	Approved
5	Thiabendazole	Pheasants	gapeworm	Approved
30	Bacitracin	Quail	Ulcerative enteritis	Approved
90	Monensin	Quail	Coccidiosis	Approved
115	Salinomycin	Quail	Coccidiosis	Approved
191	Lasalocid	Chukar partridges	Coccidiosis	Approved
137	SDM/ormetoprim	Chukar partridges	Coccidiosis	Approved
96	SDM/ormetoprim	Catfish	Bacterial infections	Approved
169	Formalin	Penaeid shrimp	External protozoan parasites	Approved
238	Formalin	Finfish and eggs	External parasites	Approved
15	Oxytetracycline	Lobster	Gaffkemia	Approved

* "PMF" indicates that the Food and Drug Administration has accepted a Public Master File but that the sponsoring pharmaceutical company has not completed the approval process allowing for a new minor species label addition.

Table 2: Active NRSP-7 research projects

ADR	DRUG	SPECIES	INDICATION	STATUS*
252	Tilmicosin	Veal calves	Respiratory Infection	Active
171	Ceftiofur	Goats	Pneumonia	Under review
33	Amoxicillin	Goats	Bacterial Pneumonia	Active
43	Oxytetracycline	Goats	Bacterial Pneumonia	Active
299	Pirlimycin	Goats	Mastitis	Active
246	Tilmicosin	Sheep	Respiratory disease	Under review
83	Oxytetracycline	Sheep	Bacterial Pneumonia	Active
258	Progesterone	Sheep	Estrus Synchronization	Active
284	MGA/GnRH	Sheep	Estrus Synchronization	Active
222	Ivermectin	Bison	GI parasites	Under review
216	Fenbendazole	Fallow deer	GI parasites	Active
294	Lasalocid	Deer	Coccidiosis	Active
107	Ivermectin	Rabbits	Ear mites	Active
235	Lasalocid	Pheasant	Coccidiosis	Active
236	Clopidol	Pheasant	Coccidiosis	Active
274	Zoamix	Pheasant	Growth/coccidiosis	Active
280	Fenbendazole	Pheasant/partridge	Gapeworm/capillaria	Active
273	Nitarsone	Partridge	blackhead	Active
18	Chloramine-T	Salmonids	Bacterial gill disease	Active
135	Erythromycin	Salmonids	Bacterial kidney disease	Active
259	Hydrogen peroxide	Various fish	Bacterial gill disease	Active
271	Carp Pituitary	Various fish	Spawning Aid	Active
295	Strontium Chloride	Various fish	Otolith marking	Active
245	Oxytetracycline	Finfish	Otolith marking	Under review
285	Oxytetracycline	Summer flounder	Vibriosis	Active
286	Oxytetracycline	Tilapia	Strep infections	Active
217	Tylosin	Honeybees	American foulbrood	Active

* "Under review" indicates that the completed PMF has been submitted to the Food and Drug Administration for review, comment and acceptance.

Table 3: Most common FARAD requests received January 1995 to June 1997

Compound	No spp.	Cattle	Swine	Horse	Goat	Sheep	Chicken	TOTAL
Penicillin	14	63	6	1	3	9		96
Flunixin	6	55	10		4	5		80
Oxytetracycline	6	58	1		3	7	1	76
Phenylbutazone	3	31	8	9	2	2		55
Gentamicin	4	40	7	1	1			53
Xylazine	11	31	1	1	1			45
Dexamethasone	1	32	7	1	2	1		44
TMS	3	20	11	2	1	2	2	41
Ivermectin	6	15	1		10			32
Acepromazine	3	19	5	1				28
Florfenicol	3	24			1			28
Enrofloxacin	8	9	5		1	1	1	25
Spectinomycin		21	2			1		24
Vitamins	6	13	1		3	1		24
Fenbendazole	4	8	1		6	3	1	23
Aspirin	3	13	3		1			20
Tetracycline	1	15	3			1		20
Iodide Sodium	1	15				2		18
Ketamine	8	7	1			2		18
Ceftiofur	1	11			1	3		16
Chlorhexidine	1	14		1				16
Chlortetracycline		14	2					16
Ampicillin	2	8	2		3			15
Griseofulvin		7			2	6		15
Ketoprofen	1	11	1		1	1		15
Amoxicillin	2	4	6		2			14
ECP	1	12				1		14
Eythromycin	1	11	1		1			14
Sulfadimethoxine	2	4	1		3	3	1	14
Albendazole	1	3			4	2	2	12