THE FARAD NEWSLETTER

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

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IN THIS ISSUE:

1. FROM THE EDITOR

This issue addresses several issues for which there is particular liability for practitioners and producers. The nitrofurans have been added to the "prohibited" list for food animals and phenylbutazone may follow. Treatment with these compounds has resulted in large-scale condemnation of product and intense regulatory scrutiny. Also in this issue you will read that, increasingly, producers who habitually offer contaminated animals for sale are appearing in Federal court to sign "consent decrees" requiring them to institute onerous and expensive management changes. Producers who violate these court orders face steep fines and even jail time. I have assisted four dairies in this situation and am confident in saying it is a situation no producer or practitioner wants to be in. Now might be a particularly good time for veterinarians to review drug use and storage on each of their farms. As always FARAD stands ready to assist you however we can.

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2. TOPICAL NITROFURAN USE PROHIBITED IN FOOD ANIMALS

Effective May 7, 2002 the Food and Drug Administration (FDA) will prohibit the use of topical nitrofuran-containing drugs in food-producing animals. Historically nitrofurazone and furazolidone were approved for a variety of protozoal and other infections in poultry and swine. In 1991, based on demonstrated carcinogenicity in laboratory animals and the absence of a reliable detection method, the FDA withdrew approval for systemic animal nitrofuran products. A limited number of topical nitrofurazone products however, labeled for "pinkeye in cattle, sheep and goats" and "surface wounds, cuts and abrasions on all livestock" remained available. These included furazolidone aerosol powder (examples: Topazone and Furox) and nitrofurazone topical powder (examples: NFZ Puffer and P.E. 7). As a result of a FDA-sponsored study demonstrating meat and milk residues following label topical use, manufacturers of these products agreed to remove remaining food animal indications from their product labels. Topical products with "old" labels, already in distribution, were allowed to be depleted through normal commercial channels. *With this present action the use of any nitrofuran product (regardless of its label) in a food animal becomes a violation of the Food Drug and Cosmetic Act and one of FDA's highest regulatory priorities.* A number of nitrofuran-containing products are still currently available for topical or ophthalmic use in dogs, cats, and horses. These products may continue to be used in those species but may not be used

in (or on) food animals. This is a particularly important notice for practicing veterinarians. FARAD was recently consulted on a case where 34 beef cattle were treated for pinkeye with a nitrofuran "puffer" product leading to the condemnation of a large quantity of product. There are a number of alternative products with labels for pinkeye including two approved for lactating cows: Gentocin® Pinkeye Spray (Schering-Plough) and Liquamycin® LA 200 (Pfizer). The order of prohibition was published in the Federal Register: February 6, 2002, Volume 67, Number 25, Pages 5470-5471.

With the May 2002 implementation of this order, the list of drugs prohibited from extra label use in food animals (in chronological order of prohibition) will be:

Diethylstilbestrol (DES)
Chloramphenicol
Nitroimidazoles (including dimetridazole, metronidazole and ipronidazole)
Sulfonamide use in lactating dairy cattle*
Clenbuterol
Dipyrone**
The fluoroquinolones (example enrofloxacin)
The glycopeptides (example vancomycin)
Nitrofurans (including nitrofurazone, furazolidone)

*Currently the only sulfonamide available for use in dairy cattle older than 20 months of age (CVM's definition of a lactating cow) is sulfadimethoxine. This drug may only be used on-label in adult dairy cattle and therefore 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 dipyrone-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 full text of the action can be obtained using "Browse" at the Federal Register web site:
http://www.access.gpo.gov/su_docs/aces/aces140.html

The Schering-Plough Animal Health home page is:
http://usa.spah.com/home.cfm

The Pfizer Animal Health home page is:
http://www.pfizer.com/ah/

3. PHENYLBUTAZONE CONCERN CONTINUES

Veterinary products containing phenylbutazone (PBZ) are approved in the U.S. as tablets, pastes and injectables for horses and tablets for dogs. Approved also in humans, PBZ has a particularly narrow therapeutic index and in man has been associated with a variety of adverse drug reactions including fatal blood dyscrasias. In recent years during follow-up residue investigations, FDA inspectors have frequently found PBZ on dairies. Last year USDA and FDA collaborated in the development and field testing of new screening and confirmatory assays for PBZ, finding a 0.05 percent failure rate. Because no tolerance for PBZ exists in a food animal species, its detection at any level is considered an illegal residue. Should USDA continue to detect PBZ residues at slaughter, the very real possibility exists that FDA will add PBZ to the prohibited list. In the wake of a particularly high-profile state fair case where some 30,000 pounds of meat was condemned, FARAD performed an exhaustive literature review and risk assessment. For oral administration of up to 6 mg/kg (indefinite treatment duration) or a single intravenous administration of up to 10 mg/kg, FARAD recommends a 240-hour milk withdrawal and 45-day slaughter withdrawal. These withdrawal times will not be adequate following intramuscular administration or in cattle less than three months of age.

In spite of these recommendations, FARAD strongly discourages the use of phenylbutazone in any food animal. In the absence of an effective drug labeled for a given indication, veterinarians may use or prescribe extra label treatment. Extra label drug use is permitted only if it does not result in violative food residues. Food animal practitioners must preferentially select a drug with a food animal label over a human or companion animal drug if an effective food animal product is available. Practitioners must be able to support claims of ineffectiveness of a label use. From an FDA policy statement comes the following: "Unsupported claims of clinical ineffectiveness will not be allowed to circumvent the statutory prohibition against extra label drug use when an approved NAD (New Animal Drug) for that condition exists." Drug cost is not considered by FDA to be an acceptable medical rationale. With the availability of flunixin as an effective approved anti-inflammatory in cattle, it will be difficult for practitioners to supply the necessary supporting rational should the need arise.

* Payne, MA. Anti-inflamatory therapy in dairy cattle: therapeutic and regulatory considerations. *California Veterinarian*. 55(2):10-12, 2001.

JAVMA news briefs related to phenylbutazone:
http://www.avma.org/onlnews/javma/nov01/s110101g.asp
http://www.avma.org/onlnews/javma/oct00/s100100a.asp

4. NEW GENTAMICIN CATTLE URINE ASSAY AVAILABLE

Residues due to gentamicin have been increasing over the last half-decade. In 1999, (the most recent residue data available from USDA) gentamicin accounted for approximately 30% of all residues detected in cattle nationally. In one Pennsylvania slaughter plant using an aggressive sampling program, gentamicin accounted for nearly 38% of residues, out pacing even the beta lactams. Silver Lake Research has announced the availability of a new cow-side urine assay for gentamicin. The "Meatsafe Gentamicin" assay is a single use immuno-assay which takes about 10 minutes to run. Sensitivity and specificity data on the test are not yet available. The retail price of the Meatsafe Gentamicin test is $30.00 for a box of 10 tests. Boxes of 20 are $50. They are available through distributors or directly from Silver Lake Research (toll-free 888-438-1942).

USDA's 1999 residue data:
http://www.fsis.usda.gov/OPHS/red99/results.pdf

Pennsylvania slaughter plant data:
http://www.usaha.org/speeches/speech99/s99schul.html

The home page for the product is:
www.meatsafe.com

5. COURT INJUNCTIONS INCREASINGLY USED WITH PROBLEM DAIRIES

Producers unable or unwilling to prevent the sale of contaminated cattle are increasingly facing court orders, large monetary fines and even jail sentences. A typical scenario is that drug residues are detected in numerous cull cows or calves sent to slaughter by a producer. Food and Drug Administration (FDA) inspectors determine that the dairy facility and management are insufficient to protect consumer health. The producer is required to appear in a Federal District Court where he signs a "Consent Decree" agreeing that animals will not be sold off the farm until he has completed an exhaustive series of management changes.

Management changes typically required of producers under injunction include:

1. Individual and permanent identification for all animals on premises.
2. A record system containing the animal, date, drug, dose, route, person treating, withdrawal period and projected clearance date for every drug administration on the premises. In addition, records will include the culling date and buyer for every animal leaving the dairy.
3. Measures that prevent extra label use of drugs except as permitted under AMDUCA.
4. Measures that prevent the sale of treated animals prior to completion of withdrawal.

5. Creation of a written drug inventory to include the name, quantity, strength, form, date of purchase/receipt and name/address of supplier for each drug received on the premises.
6. A drug accountability system reconciles the quantity of drug purchased with that administered and remaining in inventory.
7. A quarantine or segregation system that readily distinguishes between treated and untreated animals and which prevents the sale of treatment animals prior to completion of withdrawal.
8. Written statement to purchasers that each animal has not been treated or has completed the appropriate withdrawal period as well as the treatment history and withdrawal dates for each animal. The producer obtains a signature from each purchaser documenting receipt of this information.

Prior to selling animals again, the producer must provide a written report documenting management changes and successfully complete a facility and records inspection where the FDA determines that the producer is in compliance. The producer agrees to unannounced inspections for all current or future locations where they conduct business and agrees to reimburse FDA for both court and inspection costs.

If the producer violates the consent decree (sells animals prior to the injunction being lifted) he may be charged with contempt of court in civil or criminal court. In addition to other remedies, the court could require (in addition to court costs) "liquidated damages" which could, for instance, amount to $500 per day for each day the producer was out of compliance and $5,000 for every animal sold while under injunction. In two recent cases involving California dairy producers who violated their injunctions, one producer agreed to pay $140,000 to settle contempt charges while another was given 6 months jail time.

FDA news briefs related to injunctions:
http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01137.html
http://www.fda.gov/cvm/index/fdavet/2001/Sep_Oct.htm

6. DAIRY AREAS OPEN FOR DRUG INSPECTION
The Food and Drug Administration has provided guidance about what constitutes the inspectional area of a Grade A dairy farm in relation to drug storage, labeling, and use. These areas include the milk house, milking barn, stable or parlor, adjacent storage areas, cow yard and cattle housing areas, surroundings, waste disposal areas, the water supply/ distribution system, maternity areas, animal treatment areas or hospital barns, replacement heifer areas, offices, utility rooms, tool sheds, or other areas where drugs used to treat dairy animals may be used or stored. Essentially any area on a dairy (other then personal residences or vehicles) is considered available for state or federal inspection.

For more information see JAVMA's news brief at:
http://www.avma.org/onlnews/javma/feb02/s021502l.asp

7. FDA TO REEXAMINE FLEXIBLE LABELING
The Food and Drug Administration is withdrawing a guidance for industry (#66) entitled "Professional Flexible Labeling of Antimicrobial Drugs" which was issued in August 1998. The concept behind Professional Flexible Labeling (PFL) was to allow pharmaceutical manufacturers (product sponsors) to include in product labels a range of doses and other information to assist practitioners in tailoring treatment to particular clinical situations. This guidance is being withdrawn because of concerns that its "broad indication" provision could allow for clinical applications that exceed a sponsor's ability to provide "substantial evidence of effectiveness". The agency intends to develop a new document on this topic (with particular focus of the revisions in the "Indications" and "Microbiology" sections) and invites written or electronic comments. The notice was published in the Federal Register: January 30, 2002, Volume 67, Number 20, Page 4456-4457.

The full text of the action can be obtained using "Browse" at the Federal Register web site:
http://www.access.gpo.gov/su_docs/aces/aces140.html

8. NEW RECORD-KEEPING RULES FOR FOOD & ANIMAL DRUG EXPORTERS
The Food and Drug Administration has issued a final rule, effective March 19, establishing record keeping requirements for persons exporting animal or human drugs, biological products or devices, or food or

cosmetics which may not be marketed or sold in the United States. Under the final rule, exporters of food or animal drugs must retain records demonstrating that the product meets the foreign purchaser's specifications, does not conflict with the laws of the importing country and is labeled on the outside of the shipping package that it is intended for export only. This rule will have particular application to firms which export food products into countries which have a higher tolerance for certain contaminates or drugs than does the United States. The rule was published in the Federal Register: December 19, 2001, Volume 66, Number 244, Pages 65429-65448.

The full text of the rule can be obtained using “Browse” at the Federal Register web site: http://www.access.gpo.gov/su_docs/aces/aces140.html

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