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FDA VETERINARIAN

FEEDS COMPLIANCE PROGRAM ISSUED

by Patsy Gardner

The **Feed Manufacturing Compliance Program** (7371.004) for animal feeds for 2001 - 2005 has been printed and distributed to FDA offices.

Compliance Programs are formally written plans that direct and specify the work that is done by the FDA's field personnel. They generally provide specific guidance to ensure a uniform approach for regulatory/administrative action; to accumulate data on a known problem to determine long-range trends on a statistically valid basis; and to gather product or industry information within a specific time frame to determine the existence or extent of a problem.

In the past, the Medicated Feeds Compliance Program has been limited to medicated feed manufacturing. The name was changed to Feed Manufacturing to incorporate inspectional and regulatory coverage for non-medicated and medicated feed manufacturing as needed. This change was in response to the growing concern over the safety of feed ingredients and their impact on public health. Of particular concern is the use of mammalian protein in feed for ruminants because of the possible transmission of the causative agent for Bovine Spongiform Encephalopathy (BSE). BSE is a fatal animal disease that may be linked to a fatal human disease called new variant Creutzfeldt-Jakob Disease. To help prevent the establishment of BSE in the U.S., FDA published regulations (August 4, 1997) prohibiting the use of certain mammalian protein in feed for ruminant animals. This compliance program addresses the inspection of feed manufacturing facilities to assess the firm's compliance with these regulations.


Photo by Karen Kandra

Revised guidance is now available for inspections of feed manufacturing facilities like this new mill at USDA's Beltsville Agricultural Research Center.

(Continued, next page)

CVM ISSUES FIELD ASSIGNMENT TO DETERMINE BACKGROUND DIOXIN LEVELS

BACKGROUND

In July 1997, after lengthy investigation by several Federal and State agencies, the source of the dioxin contamination in broilers was traced to a feed ingredient called ball clay. Ball clay was used as an anti-caking agent in soybean meal, in other feed components, and in complete animal feeds. CVM worked cooperatively with the affected industries across the nation to halt any further distribution and use of the feed known to be contaminated with dioxin. Ball clay is no longer accepted for use as a feed ingredient by the Association of American Feed Control Officials.

In FY 1998, FDA initiated steps to determine whether other anti-caking agents were contaminated with dioxin, similar to the findings in ball clay. Industry associations met with CVM to determine the type of information needed, which resulted in a compilation of industry sampling of anticaking agents for dioxins. FDA, with analytical assistance from EPA, also surveyed anti-caking ingredients for the presence of dioxins. As a result of this survey, CVM prepared a revised guidance document for industry (#98) entitled "Dioxin in Anticaking Agents Used in Animal Feed

(Continued, next page)

In This Issue

U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR VETERINARY MEDICINE

FEEDS COMPLIANCE PROGRAM ISSUED (Continued)

The enactment of the Animal Drug Availability Act of 1996 (ADAA) amended Section 512 (m) of the Federal Food, Drug, and Cosmetic Act to require a single facility license rather than multiple medicated feed applications (MFAs) for each feed mill as previously required. Firms using Category II Type A Medicated Articles to make medicated feeds are required to register with FDA and hold an approved medicated feed mill license. The compliance program contains information on the Medicated Feed Mill License as well as guidance on the current good manufacturing practice regulations; it also contains a list of definitions for terms used in it. The Program also contains information on verifying compliance with Veterinary Feed Directive (VFD) requirements and information for those who wish to distribute feed containing VFD drugs. The VFD is another mandate of the ADAA.

The Feed Manufacturing Compliance Program contains a completely revised Form FDA 2481, Medicated Feeds Inspection Report. The form contains questions that relate to BSE and VFDs.

For a copy of the revised program, please contact Patsy Gardner at 301-827-0187, or by e-mail at pgardner @cvm.fda.gov.

Patsy Gardner is an Industry Compliance Analyst in CVM's Division of Animal Feeds. □

CVM ISSUES FIELD ASSIGNMENT TO DETERMINE BACKGROUND DIOXIN LEVELS (Continued)

and Feed Ingredients" (Notice of Availability published in the *Federal Register* on April 19, 2000, Vol. 65, No. 76, Pages 20996-7).

FDA is a public health agency and is concerned about human exposure to dioxin and dioxin-like compounds. Certain dioxin, furan and PCB (polychlorinated biphenyl) congeners comprise a family of about 30 compounds that act by a similar mechanism. This family of compounds accumulate in the fat of humans and animals and produce a broad range of adverse effects including, but not limited to, enhanced tumorigenicity, enzyme induction, immune suppression, and a wasting syndrome. The diet is considered the primary route by which humans are exposed to these compounds and animal fats may be the greatest contributor to the dietary exposure. The remainder of this article summarizes CVM's recent efforts to obtain additional data on background levels of dioxin and dioxin-like compounds in animal feed.

CVM'S APPROACH

On May 22, 2000, CVM issued a field assignment entitled "*Preliminary National Survey of Dioxin-like Compounds in Animal Fats, Animal Meals, Oilseed Deodorizer Distillates, and Molasses.*" That assignment examined the feed ingredients suspected of containing the highest dioxin levels (fish meal, oilseed deodorizer distillates, animal fat, and meat and bone meal). It also looked at ingredients where air deposition (corn), uptake from soil (beet molasses) and fire during the harvest (cane molasses) were likely a major pathway of dioxin contamination. CVM is hopeful the EPA lab can complete the analyses on the 47 samples collected in the next few weeks.

On July 3, 2001, CVM issued a follow-up assignment entitled "*Preliminary National Survey of Dioxin-like Compounds in Oilseed Meals, Fat-soluble Vitamins, Complete Feeds, Milk Products, Minerals, and Wood Products.*" This assignment is similar to the previous assignment, except the FDA's Arkansas Regional Laboratory will conduct the analyses and the feed ingredients will be different. The feed ingredients selected in this assignment were considered to be in the second tier regarding likelihood of elevated dioxin levels. CVM realizes it is more of an art than a science when it comes to prioritizing samples for dioxin analysis, but believes it is important to discuss the major reasons why these feeds were selected.

There were several factors involved in the selection of complete feed, oilseed meals, fat-soluble vitamins, milk products, mineral products, and wood products. These factors include, but are not limited to, past history of dioxin contamination, the likelihood the ingredient would be used in a ration, the amount typically used in a ration, the percentage fat, the likelihood of having a dioxin contamination from the manufacturing process, the likelihood of having elevated dioxins at the mine of origin of the ingredient, and the need to be able to compare the results from a single ingredient with levels typically found in complete feeds.

There is very little information on background levels of dioxins in complete feed. This information will be useful if the FDA has to consider taking regulatory action on an individual feed ingredient or the total ration.

(Continued, next page)

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DR. TOLLEFSON PROMOTED TO REAR ADMIRAL

Dr. Linda Tollefson, FDA/Center for Veterinary Medicine (CVM) Deputy Director, was promoted to Assistant Surgeon General (Rear Admiral) on August 1, 2001. Dr. Tollefson is the first female veterinarian in the U.S. Public Health Service Commissioned Corps to reach the O-7 (Rear Admiral) rank.

As the CVM Deputy Director, Rear Admiral (RADM) Tollefson is responsible for all public health programs and international activities. A primary focus of the Center's mission is human food safety, through assessing the safety and effectiveness of drugs used in animals intended for human consumption. RADM Tollefson is also responsible for the management and coordination of all Center projects under the National Food Safety Initiative. The Food Safety Initiative is designed to reduce the incidence of foodborne disease through extensive collaboration among the U.S. Federal food safety agencies, State governments, and private organizations.


Photo by Catherine Brown

Dr. Linda Tollefson

RADM Tollefson is one of the founders of the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS). NARMS monitors development of resistance in zoonotic enteric pathogens isolated from human and animal clinical specimens, from carcasses of food-producing animals at slaughter, and from retail food. NARMS was established in 1996 as a collaboration among several Federal agencies in response to concerns associated with the approval of antibiotics for use in food animals that are important for human medical therapy. The data generated from NARMS and follow-up outbreak investigations are used by several Departments and multiple agencies and are vital to the mission of the Public Health Service and to the health of the entire population.

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CVM ISSUES FIELD ASSIGNMENT TO DETERMINE BACKGROUND DIOXIN LEVELS (Continued)

Oilseed meals are commonly used at levels greater than 10% of the diet in many animal species. While oilseed meals are primarily utilized for their high levels of crude protein (about 25-50%), they also contain some fat (about 1.5-8.0% depending an whether the fat is solvent or mechanically extracted). The oilseed meals could also potentially pick up dioxins during the manufacturing process or when anti-caking agents are mixed with them.

Additional information on dioxins in fat-soluble vitamins (A, D, E, and K) is important for the following reasons: 1) the fat-soluble vitamins are commonly added at low levels to most animal diets, 2) dioxins are fat-soluble compounds, and 3) there is a wide diversity in how fat-soluble vitamins are derived. Some of these vitamins are synthesized. Some are derived from plants and some come from animals.

While milk and milk products for human consumption have been tested for dioxins by the FDA's Center for Food Safety and Applied Nutrition, there is little, if any, data on dioxins in milk products used in animal feeds. Dried whole milk should contain a minimum of 26% fat and condensed buttermilk and dried cheese often contain about 15-25% fat. In addition to these "fatty" milk products, there are several milk products (casein, whey, skimmed milk, etc.) with low levels of fat (around 1%). Since dioxins are fat soluble compounds, a slightly greater emphasis will be placed on the "fatty" milk products than on the "non-fatty" ones.

The potential concerns with mineral products are two-fold. First, they may be like ball clay and contain high dioxin levels from their mine of origin. Second, the manufacturing process, transport and/or prior use of these mineral products may have introduced some dioxin contamination.

The potential concern with wood products (cellulose, lignin, etc.) is that the starting material could have been treated with pentachlorophenol (PCP). PCP was a wood preservative whose uses were greatly curtailed because of its high dioxin contamination. Elevated dioxin levels were recently found in choline chloride from the EU and additional analyses indicated that a carrier, pine sawdust, was the likely source of the contamination. The congener pattern in the pine sawdust was consistent with prior PCP treatment.

There are no tolerances established by the FDA for dioxins and furans in food or feed. Temporary tolerances for PCBs for feed and foodstuffs can be found in 21 CFR 109.30 and 509.30. FDA, in conjunction with the USDA, EPA, CDC and the European Union, is addressing both international and domestic dioxin, furan and PCB concerns.

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DR. TOLLEFSON PROMOTED TO REAR ADMIRAL (Continued)

Prior to becoming CVM's Deputy Director, RADM Tollefson served as Director of the Center's Office of Surveillance and Compliance. In that capacity, RADM Tollefson was responsible for all FDA surveillance, regulatory compliance, and enforcement activity related to veterinary medical drugs and devices and all activities, both pre-market and post-market, for FDA's animal feed safety program.

Before joining the Center for Veterinary Medicine in 1993, RADM Tollefson was Chief of the Epidemiology Branch in the Center for Food Safety and Applied Nutrition. The Branch provides epidemiology support and expertise to all functions of the Center, including issues of foodborne disease, chemical contamination, use of epidemiology data for risk assessment, and surveillance of adverse reactions to food products and food and color additives.

RADM Tollefson was responsible for the development and implementation of the Center's Adverse Reaction Monitoring System, a post-marketing surveillance system that monitors adverse health effects associated with food products and food and color additives. While Chief of the Epidemiology Branch, RADM Tollefson also served as co-chair of the Center's Health Hazard Evaluation Board. The Board evaluates possible microbiological and environmental contamination of food and cosmetics, serves as the Institutional Review Board for the Center, and assists other Federal and State government agencies in providing assessments of health hazards.

A native of Indiana, RADM Tollefson earned a Bachelor of Science degree in 1976 and a Doctor of Veterinary Medicine degree in 1980 from the University of Illinois, and a Master of Public Health degree from The Johns Hopkins University in 1984 with special training in epidemiology and biostatistics. RADM Tollefson has authored numerous scientific articles and book chapters. She earned Exceptional Capability Promotions to both the O-5 and O-6 grades and received many Public Health Service honors and awards, including the Meritorious Service, the Outstanding Service, and the Commendation Medals, for her leadership in epidemiology and public health surveillance. RADM Tollefson is currently president-elect of the American Association of Food Hygiene Veterinarians.

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UPDATE ON LIVESTOCK CLONING

FDA's Center for Veterinary Medicine (CVM) has received numerous inquiries about livestock cloning. This article provides information about CVM's activities in this area.

CVM is considering the safety of animals and their progeny that are produced as a result of somatic cell nuclear transfer (also known as somatic cell clones or NT clones). "Dolly the Sheep" is the most famous animal produced in this manner, but the technology also has been applied to rodents, cattle, swine, and other species. It involves removing the nucleus of a cell from an adult animal that will be copied and inserting it into an animal egg whose nucleus has been removed. The resulting embryo is implanted into a surrogate mother that carries the fetus to term. In evaluating animal cloning, CVM's first priority is to examine the safety of food products (e.g., meat, milk, eggs) from animals developed through somatic cell cloning but are otherwise unmodified.

CVM has been interested in cloned animals for some time. Last fall, when it became evident that commercial ventures were developing somatic cell clones for use in breeding food-producing animals, CVM contracted with the National Academy of Sciences (NAS) to conduct an independent, scientific peer review of available safety data on cloned animals and the food derived from them. This review, including the safety of cloning to the animals and environment as well as any food derived from the animals, will help CVM decide how these animals should be regulated, including whether there may be circumstances in which CVM ordinarily would not need to exert its authority.

The NAS expert Committee on Defining Science-Based Concerns Associated with the Products of Animal Biotechnology is planning to hold a public meeting this fall to discuss this issue and to elicit safety information from the scientific community. CVM has contacted companies known to be developing cloned animals to inform them that the Center is considering this issue, and to encourage their contributions to this public meeting. Until the Center has scientific information on safety, the Center for Veterinary Medicine has been asking the companies not to introduce these cloned animals, their progeny, or their food products (such as milk or eggs) into the human or animal food supply. CVM has asked the companies to participate in the NAS public meeting, and to be prepared to supply scientific information they have collected on the safety of cloned animals. Any companies involved in livestock cloning that have not yet contacted CVM are encouraged to do so. They may contact Mr. John Matheson at: clones@cvm.fda.gov or by calling 301-827-5895.

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CVM SCIENTIST CELEBRATES 50 YEARS AT FDA

CVM congratulates Dorothy (Dottie) Wintermere Pocurull on her celebration of 50 years of Federal Government service.

Dottie reached this milestone on January 14, 2001, and was recently recognized at a ceremony at the Department level by HHS Secretary Tommy Thompson and Deputy Secretary Claude Allen.

Born in Bayonne, New Jersey, the only child of a Scottish mother, and an English father, Dottie's family settled in Bowie, Maryland when she was a young girl. She attended Bladensburg High School, and earned both B.S. and M.S. degrees in Bacteriology from the University of Maryland.

With her scientific training, Dottie joined FDA in 1948 as an antibiotics analyst with the Penicillin Control and Immunology Plate Assay Section. This group was responsible for the certification of penicillin and streptomycin by microbiological and chemical assays. As this area expanded, Dottie's duties included methods development and research. She published several manuscripts related to this research.

Dottie took a 3-year break in service following the birth of her first child. After her return to the antibiotic certification division in a research position, she spent four years as a supervisor in the assay laboratories. During this period, the laboratories moved into the newly built FOB-8, at that time considered a state-of-the-art science building.

In 1967, Dottie moved to a microbiologist position at FDA's Beltsville, Maryland facilities on the USDA's Agricultural Research Farm. Known as the Division of Veterinary Medical Research (DVMR), this group had begun experiments to determine the antibiotic resistance patterns of various animal species, a fascinating and resource intensive effort.

In 1979, Dottie took a detail in the Document Review Branch of the Bureau of Veterinary Medicine (BVM) in Rockville, Maryland, and in 1980, she accepted a permanent position with the Bioresearch Monitoring Program.

Dorothy Pocurull accepts 50-year plaque from HHS Deputy Secretary Claude Allen

Currently, Dottie is a member of the Bioresearch Monitoring and Administrative ActionsTeam in CVM's Division of Compliance. Major responsibilities include disqualification of clinical investigators, withdrawal of approved drugs, termination of investigational new animal drug applications, and revocation of medicated feed licenses.

Dottie has witnessed many changes in FDA, especially the recognition of women as equal scientific colleagues. At the time she entered BVM, there were only two professional women employed.

Dottie has no plans to retire since she believes that working keeps the mind and body active. Dottie has a son, Edward, employed by the Computer Center at NIH, and a daughter, Isabel, employed at CVM's Division of Animal Feeds. In addition, she has a granddaughter who attends the University of Maryland. Dottie is an inspiration to all of us at CVM.

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CVM AQUACULTURE TEAM TOURS CATFISH FARMS

by Susan Storey, D.V.M.

In May, members of the Aquaculture (AQ) Drugs Team of CVM's Division of Therapeutic Drugs for Food Animals took a minisabbatical to Mississippi and Arkansas to learn about the farm-raised catfish industry. Members of the AQ Drugs Team include Joan Gotthardt, D.V.M.—Team Leader, Mr. Ben Puyot-Consumer Safety Officer, and Don Prater, D.V.M. and Susan Storey, D.V.M.—Veterinary Medical Officers. Mr. Hugh Warren, Executive Vice President of the Catfish Farmers of America (CFA) organized the tour. Mr. Warren is a long-time resident of the Greenwood, Mississippi area and has been in his current position for about 12 years. Rosalie "Roz" Schnick, the National Aquaculture NADA Coordinator since 1995, accompanied the AQ team on the tour.

The team learned a lot of basic information about the catfish industry as well as more specific information about the catfish industry in the Mississippi Delta. Catfish are the number one farmed finfish in America. More catfish are produced in the U.S. annually than all other farmed fish combined. Mississippi, Arkansas, Alabama, and Louisiana produce 95% of the U.S. farm raised catfish with ponds covering 140,000 acres of these 4 states. The single largest catfish farm has 8,000 acres of ponds. The farm-raised catfish industry contributes $2 billion to the Mississippi economy annually.

Catfish in the Mississippi Delta are raised in levee-type ponds in fresh

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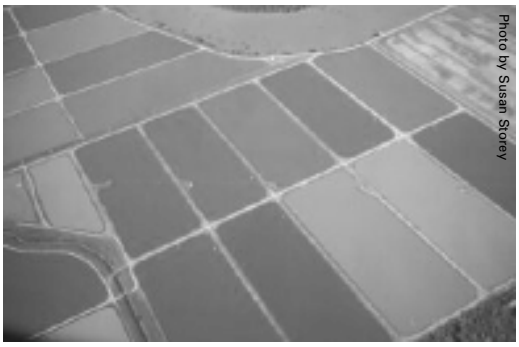

Aerial view of ponds

water from underground wells. The clay-based soil of the region provides an excellent substrate to build the levees and to retain the water in the ponds. The ponds average 10 to 20-acres in size with most ponds being closer to 20 acres. The 20-acre size is a compromise between ease of management and the cost of construction. One company farm the team visited had recently drained several ponds after more than 10 years in production in order to rebuild the levee walls. A company representative indicated that most of the farm's 20-acre ponds would eventually be divided into 10-acre ponds. The representative stated that the 10-acre ponds would be easier to feed and harvest and the wind would cause less wave action and therefore less erosion of the levees. The estimated cost of building the levee to divide a pond is $20,000.

Most ponds are rectangular, but can be other shapes depending on topography and property lines. Pond depth averages 4 to 6 feet with a shallow end and a deep end to assist drainage. Ponds are seldom completely drained. Ponds are drained by gravity through a pipe that empties into a ditch. The drains and ditches are designed to maintain the water level at no higher than 1-1/2 feet below the top of the levee. The drainpipe must also keep the catfish in the pond and other fish species out. Ponds are harvested year round and the average 20-acre pond produces 4,200 pounds of catfish yearly.

The first day of the tour included an aerial overview of catfish ponds in the Mississippi Delta. Many areas have ponds as far as the eye can see. What is really noticeable from the air is not only the varied shape and size of the ponds, but also the varied color of the ponds. The ponds can be blue, green, brown, or any combination of these colors. Agitated pond sediments and algae are thought to be the main determinants of water color. Often ponds that are managed identically look very different.

Following the aerial overview, the team visited the USDA-Agricultural Research Service's Harry K. Dupree – Stuttgart National Aquaculture Research Center (SNARC) in Stuttgart, Arkansas. Donald Freeman, Ph.D., the director of the Center, outlined the research initiatives of SNARC. Mr. Billy Griffin, microbiologist, led a tour of the Center. SNARC was originally established in 1958 and dedicated in 1962. Its purpose was to develop a program of research and experiments to solve problems related to the production and harvest of warm-water fish. The Center was transferred to the USDA from the Department of the Interior in 1996. In 1992 an 18,000 square foot building was completed with 60% of the building devoted to research labs. Many of the laboratories have recently been equipped with state-of-the-art equipment needed for the research performed at SNARC. The Center also has a 3,700 square foot building with 72 aquaria and numerous troughs and tanks. An 8,000 square foot covered "tank farm" contains 120 four-foot diameter fiberglass fish tanks as well as a small hatchery area. Outside are seventy-two tenth and quarter-acre ponds, nine 1.0-acre ponds, two 1.5-acre earthen raceways, a 3-acre holding pond and a 27-acre reservoir. Three wells supply the water for the tanks and ponds, at a rate of up to 2,500 gallons per minute. The Center has a water treatment plant to handle all discharges and has equipment to manufacture pelleted fish feed needed for research projects.

Research at SNARC is primarily on warm-water fish species other than catfish including striped bass, tilapia, carp, eels, ornamental species, and baitfish. Studies have been done evaluating the safety and efficacy of aquaculture therapeutics and determining therapeutic drug residues in the edible tissues of fish. SNARC is also working to develop practical diets for hybrid striped bass and other fish species. During nutrition studies researchers measure fillet yield, feed conversion, and body composition. Recent research has been done to determine the physical and chemical factors that maximize production of zooplankton, an important source of oxygen in the pond and food for some stages of development of some species of fish. Researchers are attempting to develop management practices for year-round pond production of zooplankton.

Another area of research at SNARC, as well as a large concern for the catfish industry in MS, is bird depredation. Pond culture systems provide ideal habitats for many migratory birds. Double-crested cormorants, American white pelicans, ducks, herons, and egrets create substantial loss from the ponds. To disperse the birds many types of nonlethal harassment have been tried, but with limited success. Since 1972, AL, AR, LA, and MS have seen increased recoveries of cormorants banded in breeding areas as young birds. SNARC purchased satellite transmitters that researchers from the National Wildlife Research Center (MS Research Station), in cooperation with USDA's Wildlife Services programs in LA, AR, MS, and AL, placed on fifty cormorants captured from November 1999 to March 2000 and from October 2000 to March 2001. The transmitters allow researchers to determine where individual birds move during the winter, where the bird breeds in the spring, and the bird's migration path. Data received last winter, the first year of the study, indicate that double-crested

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cormorants wintering near southeastern catfish farms have a broad breeding distribution. The cormorants breed anywhere from southern Manitoba, Canada, to northern New York State. The information collected will aid the determination of how best to manage a cormorant population in which individual birds can live up to twenty years producing two young per year.

A relatively recent problem in the Delta has been the rapid spread of the digenetic trematode, *Bolbophorus confusus*. Mr. Andrew Mitchell, a researcher at SNARC, explained that pelicans carry the trematode. The ram's horn snail (*Planorbella trivolvus*), a normal inhabitant of the ponds, serves as the intermediate host for the trematode which then infects the catfish. The trematode kills numerous fingerlings every year, slows the growth of surviving catfish, and makes infected fish unmarketable because the parasite matures in the muscle of the fish. Mr. Mitchell investigated copper sulfate as a safe and effective method to reduce the number of snails in the ponds. Copper sulfate has been granted EPA registration to control snails around the perimeter of ponds. Mr. Mitchell is also considering studies with therapeutics that may be administered to the catfish to reduce the number of trematodes in the fish.

After returning to Greenwood, MS, the next stop on the tour was Thompson Fisheries. Thompson's is a catfish hatchery in Thornton, MS. Mr. Bobby Thompson started the hatchery in 1959. Today Mr. Thompson's son, Louie Thompson, runs the business. The hatchery produces 5-6 billion fry (young fish) annually. The catfish spawn in ponds from mid-April to July. Catfish lay their eggs either in or under something. At Thompson's, the fish are provided with surplus ammunition cans. The cans are checked by hand for eggs every 3 days. The egg masses are placed in baskets in special tanks in which the water is continuously circulated around the eggs. The egg masses must be handled carefully to prevent dead eggs, which are susceptible to bacterial and fungal infections. Healthy eggs hatch in about 5 days. Once hatched, fry are transferred to progressively larger tanks. Wells supply the fishery's water. A 1,700-foot deep artesian well produces 90 °F water and a second well produces cooler water that is added to provide the correct temperature water for the tanks. The fry are maintained and fed in the tanks for approximately 6 weeks. When the fry are swimming and feeding well, they are transferred to ponds. Mr. Louie Thompson estimated that 90% of the eggs hatch, however a substantial number of fry are lost in the first two days after transfer to the ponds. The hatchery sells both fry and fingerlings (3-4 inch fish) to producers. Young catfish are transported in specially designed trailers with large tanks supplied with oxygen during transport. One trailer can transport up to 1,000,000 fish at one time. A newer trailer is large enough to transport up to 2,000,000 fish at one time. Once delivered, the fish are stocked in ponds and reach a market size of approximately 1-1/2 pounds in 18 months.

The second day of the tour started at SouthFresh Farms™ a producer of farm-raised, grain-fed catfish in the Mississippi Delta since 1976. In 1980, SouthFresh constructed 640 acres of ponds in Morgan City, MS. In 1988, a processing plant was built for the farm. At that time, the plant was processing 50,000 pounds of catfish weekly. The farm was expanded to 1,615 acres of ponds in 1990 and in 1995 the capacity of the processing plant was increased to 500,000 pounds per week. In 1999 SouthFresh Farms™ merged with Alabama Farmers Co. providing a 780-acre fingerling farm and a feed mill. With this merger, SouthFresh Farms™ became a vertically integrated company, owning and managing the catfish from source to finished product. A new state-of-the-art processing plant, capable of processing 500,000 pounds of catfish weekly, was just completed in Alabama.

Mr. Julian Allen, chairman of SouthFresh Farms™, led a tour of one of the SouthFresh farms. As well as the ponds, the farm also has an on-site hatchery. A small office in the hatchery building houses the control center of the farm. Information about each individual pond is maintained on a computer in that office. The amount of feed for each pond is calculated and transmitted directly to a computer system in the truck that delivers feed to the pond. The number and size of the catfish as well as the pond temperature determine the amount of feed delivered to the pond. After sunset and throughout the night, workers measure oxygen levels in the ponds every 1-2 hours. The oxygen levels are transmitted to the computer. The farm manager monitors the oxygen levels to decide when to turn on pond aerators and how many aerators are needed in each pond. Most catfish ponds have one or two stationary aerators. Stationary aerators are electric, float on pontoons and have a large number of paddles attached to a central shaft. When on, the paddles agitate the water, adding oxygen to the water. Most farms also have aerators operated by tractors. These aerators can be moved from pond to pond as needed.

Mr. Rivers Myers III, president of SouthFresh Farms™, conducted the tour of the processing plant in Baird, MS. Prior to harvesting, farmers bring samples of their catfish to the plant. The fish are taste tested by professional tasters to prevent "off-flavor" fish from reaching the consumer. Catfish fillets should appear an opaque white when raw and have a mild, delicate taste when cooked. The catfish are individually graded for size on entering the plant. The processing machines are all automated and set to handle certain size fish. Separate machines dehead and eviscerate the fish, skin and fillet the fish. Fish that are too large must be

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hand filleted. With two operators a fillet machine can process 24 fish each minute. The fillets are quickly frozen within 30 minutes to retain the original quality of the fish. The freezing takes place in a spiral freezer with a variable speed belt regulated so that the fillets are in the freezer the correct amount of time.

The team next visited Harvest Select Farm, a broodfish and research farm in Inverness, MS. Harvest Select works to improve the genetics of catfish through research and natural selection and has 492 acres of ponds. The company helped develop a new strain of catfish, NWAC-103. The first shipment of this catfish strain was in February 2001. Nagaraj G. Chatakondi, Ph.D., a research coordinator in the aquaculture division, explained his current work with a blue catfish-channel catfish hybrid. The hybrid catfish are more aggressive eaters, grow faster, and are more resistant to certain bacterial infections. Dr. Chatakondi's main research concerns improving spawning and subsequent hatching of eggs.

While at Harvest Select the AQ team saw a pond being harvested. The pond had already been seined and the fish confined in the "sock". A seine is a weighted net that stretches across the pond and from the surface to the bottom of the pond. The nets have different size holes to keep the desired sized fish in while letting smaller fish swim out. The ends of the seine are attached to the "sock", a circular net, in one corner of the pond. The fish are swum into the "sock" and left for at least two hours to give the smaller fish time to swim out. Fish are transferred from the sock to the transport truck in a large basket operated by a crane and are weighed in the basket. The transport trucks have multiple, oxygenated tanks, so that the fish are delivered alive.

The last day of the tour was spent at the Thad Cochran National Warmwater Aquaculture Center (NWAC) and the Delta Western Feed Mill. The NWAC is located at the Delta Research and Extension Center in Stoneville, MS. The NWAC, USDA Agricultural Research Service, Mississippi Agricultural and Forestry Experiment Station, Mississippi State University Extension Service and MSU College of Veterinary Medicine serve as the base of the U.S. catfish research and extension service. The primary mission of NWAC is to combine research, extension and diagnostic services to provide solutions to the most pressing problems of the aquaculture industry. Patricia Gaunt, D.V.M., Ph.D., assistant professor MSU-CVM, led the tour of NWAC. NWAC has 243 earthen ponds from 0.1 to 9 acres totaling 180 water acres. The team met David Wise, Ph.D. and saw some of the research projects he had set up in and around the ponds. Dr. Wise investigates catfish diseases and is currently developing infection models for some of these diseases. The team also toured the fish diagnostic labs. The lab, run by Lester Khoo, V.M.D., Ph.D., provides diagnostic support for the research projects and the catfish farmers in Mississippi. Dr. Khoo demonstrated necropsy methods on catfish brought in by local farmers. The catfish were suspected to have enteric septicemia of catfish (ESC) caused by *Edwardsiella ictaluri*. ESC is the most devastating bacterial infection in catfish. Infections generally occur in the spring and fall of the year. The infection can quickly kill all the fish in a pond. Mr. Tim Santuci, Medical Technologist, demonstrated culture and identification techniques for *E. ictaluri*, which only grows at 25-30 °C.


Photo by Roz Schnick

Pond harvest at Harvest Select Farm, Inverness, MS. The fish are transferred from the "sock" to tanks on a live haul truck.

Mr. Dwayne Holifield, B.S., manager of the research farm led the tour of the Delta Western Feed Mill in Indianola, MS. Delta Western Research Center has several tenth-acre ponds. The ponds are used for research projects involving nutrition and field trials of therapeutic products. The research center also has a second mill used to produce smaller lots of experimental catfish feeds. The research unit works extensively with NWAC. The main mill produces about 230,000 tons of catfish feed annually representing thirty percent of the 825,000 tons of catfish sold annually. Railroad lines bring grain products used in the feed directly to the mill. Three large warehouses store ground corn, wheat middlings and soybean meal that are pumped directly into the mill as needed. The mill has doubled its finished-feed storage capacity over the last two years to a capacity of 5,000 tons. The mill operates two 8 - 10 hour shifts depending on the time of year. The storage area is filled completely by the end of the second shift and emptied by mid-morning the next day. The feed is delivered to farms in large tanker type trucks. Each truck has a capacity of 20 tons and can be completely filled in 2 1/2 minutes.

The mill produces a floating pellet type feed. Farm-raised catfish feed at the top of the ponds. These catfish are not the bottom feeders catfish are traditionally thought to be. Corn, wheat mids, and soybean meal are cooked, under pressure, at 190-300

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CVM AQUACULTURE TEAM TOURS CATFISH FARMS (Continued)

°F and steam is added to produce mash. The mash is forced through a die with holes sized to produce the proper pellet size. A sudden decrease in pressure after extrusion causes vaporization of part of the water and the pellet expands. The pellets are then placed in driers with the capacity to hold up to 20 tons of feed to produce the final floating pellet product.

The aquaculture team did not spend all their time looking at and learning about catfish. They also sampled quite a bit of catfish. SNARC and SouthFresh Farms™ both hosted lunches featuring traditional southern fried catfish and all the requisite side dishes. The team also tried blackened catfish and lemon pepper catfish at the Crystal Grill, a well-known restaurant in Greenwood, MS. Dr. Gaunt made sure the team had lunch at the famous Crown Restaurant. The Catfish Allison is required eating for those who have never been to the Crown. The acquaculture team did not come home hungry.

Dr. Susan Storey is a Veterinary Medical Officer with CVM's Aquaculture Drugs Team in the Office of New Animal Drug Evaluation. □

ANTIMICROBIAL SUSCEPTIBILITY PATTERNS FOR SALMONELLA ISOLATES OF ANIMAL ORIGIN, NARMS 1999

M. Headrick, L. Tollefson (FDA-CVM, Rockville, MD); *P.J. Fedorka-Cray, J.T. Gray, J. Hermosilla, J. Eubank* (USDA-ARS-RRC, Athens, GA); *D.A. Dargatz* (USDA-APHIS-VS-CEAH, Fort Collins, CO)

The following is an abstract from a poster presented at the American Society of Microbiologists (ASM) Meeting held May 20 - 24, 2001, in Orlando, FL.

Abstract

The National Antimicrobial Susceptibility Monitoring System – Enteric Bacteria (NARMS-EB) was established to provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in zoonotic enteric pathogens from human and animal populations. *Salmonella* was chosen as the sentinel organism. As part of the 1999 study, 8,508 *Salmonella* isolates of animal origin were tested against 17 antimicrobial drugs using a Sensititre™ custom designed microtiter plate. Minimal inhibitory concentrations (MICs) were determined for all antimicrobials. Animal sources of isolates included cattle, swine, chickens, turkeys, exotics, horses, dogs, and cats. These isolates were from both diagnostic and non-diagnostic submissions. Overall, all isolates were susceptible to Ciprofloxacin. The following percent sensitivity was observed for all other antimicrobials—Amikacin (>99.9%), Amoxicillin/clavulanic acid (88.4%), Ampicillin (81.9%), Apramycin (98.9%), Ceftiofur (96%), Ceftriaxone (97.7%), Cephalothin (92.3%), Chloramphenicol (90.1%), Gentamicin (90.8%), Kanamycin (87.7%), Nalidixic Acid (98.8%), Streptomycin (69%), Sulfamethoxazole (71.1%), Tetracycline (64.8%), and Trimethoprim/sulfa (96.6%). Breakpoints are not available for Florfenicol but the MIC_{50} and MIC_{90} were 4 and 8 ug/ml, respectively. For all antimicrobials, isolates collected from raw product were more susceptible than diagnostic isolates. One hundred twenty-five different serotypes were identified and the 5 most common serotypes were S. typhimurium (including var. copenhagen, n=1562), S. montevideo (n=618), S. heidelberg (n=602), S. kentucky (n=593), and S. derby (n=515). Overall, S. typhimurium had higher resistance to more antimicrobials followed by S. heidelberg and S. derby. These data provide information which can be used to analyze the development of resistance over time when compared to previous years. □

RUMINANT FEED (BSE) ENFORCEMENT ACTIVITIES

To help prevent the establishment and amplification of BSE through feed in the United States, FDA implemented a final rule that prohibits the use of most mammalian protein in feeds for ruminant animals. This rule, Title 21 Part 589.2000 of the *Code of Federal Regulations*, became effective on August 4, 1997. To date, active monitoring by the U.S. Department of Agriculture (USDA) has found *no cases* of bovine spongiform encephalopathy (BSE) in U.S. cattle.

This is an update on FDA enforcement activities regarding the ruminant feed (BSE) regulation. FDA previously provided information on this issue in CVM UPDATEs on January 10 and March 23, 2001.

FDA's enforcement plan for the ruminant feed regulation includes education, as well as inspections, with FDA taking compliance actions for intentional or repeated non-compliance. As part of the enforcement plan, an initial inspection assignment was issued to all FDA District Offices in 1998 to conduct inspections of 100% of all renderers and known feed mills to determine compliance. Additional assignments have been issued to FDA District Offices regarding (1) further initial inspections of previously unknown firms potentially handling materials prohibited in ruminant feed and (2) re-inspections of firms found on initial inspection to be out of compliance with this regulation.

FDA's CVM has assembled data from the inspections that have been conducted AND whose final inspection report has been submitted to CVM (i.e., "inspected/reported") as of June 12, 2001. There is a lag time between the completion of an inspection and the submission of a final inspection report to CVM. This lag period includes the time required to conduct quality assurance on the report and to evaluate the findings before a final report is submitted.

As of June 12, 2001, CVM had received inspection reports covering

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inspections (both initial inspections and re-inspections) of 9,867 different firms. The majority of these inspections (around 80%) were conducted by State officials under contract to FDA and the remainder by FDA officials.

Various segments of the feed industry had different levels of compliance with this feed ban regulation. The results to date are reported here both by "segment of industry" and "in total".

RENDERERS

(These firms are the first to handle rendered protein and send materials to feed mills and ruminant feeders.)

- Estimated number of rendering firms in the U.S. – **264**
- Number of firms that have received an initial inspection – **264**
- Number of firms whose initial inspection has been reported to CVM – **241**
- Number of firms handling materials prohibited for use in ruminant feed – **183** (76% of those firms inspected/reported).

Of the 183 renderers handling prohibited materials, at their most recent inspection (could have been an initial or a follow-up inspection):

- **17 (9%)** had products that were not labeled as required
- **8 (4%)** did not have adequate systems to prevent co-mingling
- **3 (2%)** did not adequately follow record keeping regulations
- **25 (14%)** firms were found to be out of compliance (some firms were out of compliance with more than one aspect of the rule)

FDA LICENSED FEED MILLS

(FDA licenses these mills to produce medicated feed products. This licensing has nothing to do with handling prohibited materials under the feed ban rule: 21 CFR 589.2000. A license from FDA is not required to handle materials prohibited under 21 CFR 589.2000.)

- Estimated number of FDA licensed feed mills in the U.S. – **1,240**
- Number of firms that have received an initial inspection – **1,240**
- Number of firms whose initial inspection has been reported to CVM – **1,176**
- Number of firms handling materials prohibited for use in ruminant feed – **435** (37% of those firms inspected/reported)

Of the 435 licensed feed mills handling prohibited materials, at their most recent inspection (could have been an initial or a follow-up inspection):

- **47 (11%)** had products that were not labeled as required
- **45 (10%)** did not have adequate systems to prevent co-mingling
- **8 (2%)** did not adequately follow record keeping regulations
- **76 (17%)** firms were found to be out of compliance (some firms were out of compliance with more than one aspect of the rule)

FEED MILLS NOT LICENSED BY FDA

(FDA does not know the total number of these feed mills because they are not required to be licensed by FDA.)

- Estimated number of feed mills not licensed by FDA in the U.S. – **6,000 - 8,000**
- Number of firms whose initial inspection has been reported to CVM – **4,783**
- Number of firms handling materials prohibited for use in ruminant feed – **1,580** (33% of those firms inspected/reported)

Of the 1,580 feed mills not licensed by FDA handling prohibited materials, at their most recent inspection (could have been an initial or a follow-up inspection):

- **312 (20%)** had products that were not labeled as required
- **169 (11%)** did not have adequate systems to prevent co-mingling
- **85 (5%)** did not adequately follow record keeping regulations
- **421 (27%)** firms were found to be out of compliance (some firms were out of compliance with more than one aspect of the rule)

OTHER FIRMS INSPECTED

(Examples of such firms include: ruminant feeders, on-farm mixers, protein blenders, and distributors.)

- Estimated number of such firms in the U.S. – **unknown**
- Number of firms whose initial inspection has been reported to CVM – **4,094**
- Number of firms handling materials prohibited for use in ruminant feed – **621** (15% of those firms inspected/reported)

Of the 621 such firms handling prohibited materials, at their most recent inspection (could have been an initial or a follow-up inspection):

- **84 (14%)** had products that were not labeled as required
- **25 (4%)** did not have adequate systems to prevent co-mingling
- **29 (5%)** did not adequately follow record keeping regulations
- **110 (18%)** firms were found to be out of compliance (some firms were out of compliance with more than one aspect of the rule)

TOTALS (as of June 12, 2001)

- Number of firms whose initial inspection has been reported to CVM – **9,867**
- Number of firms handling materials prohibited for use in ruminant feed – **2,653** (27% of those firms inspected/reported)

Of the 2,653 firms handling prohibited materials, at their most recent inspection (could have been an initial or a follow-up inspection):

- **431 (16%)** had products that were not labeled as required

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- **222 (8%)** did not have adequate systems to prevent co-mingling
- **112 (4%)** did not adequately follow record keeping regulations
- **591 (22%)** firms were found to be out of compliance (some firms were out of compliance with more than one aspect of the rule. These 591 firms will be re-inspected in the near future.)

RE-INSPECTIONS

When firms are found to be out of compliance with the feed ban rule, FDA lists them for a re-inspection. As of June 12, 2001, reports of 1,251 re-inspections have been submitted to CVM. On re-inspection of these 1,251 firms, 106 (8%) were found still to be out of compliance with this rule. Firms previously found to be not in compliance have corrected problems through a variety of ways, including further training of employees about the rule, developing systems to prevent co-mingling, re-labeling their products properly, and adhering to record keeping regulations. Other firms have achieved compliance by eliminating prohibited materials from their operations. □

TAKING THE BITE OUT OF FLEAS AND TICKS

by Linda Bren

*This article appeared in the July/August 2001 issue of the **FDA Consumer**.*

Fleas are truly devoted to their work. In one day, a single flea can bite your cat or dog more than 400 times. During that same day, the flea can consume more than its body weight of your pet's blood. And before it's through, a female flea can lay hundreds of eggs on your pet, ensuring that its work will be carried on by generations to come.

Flea bites may be merely a nuisance to some pets, but to others, they can be dangerous. They can cause flea allergy dermatitis—an allergic reaction to proteins in flea saliva. A pet's constant scratching to rid itself of fleas can cause permanent hair loss and other skin problems. A pet can get a tapeworm if it eats a flea that has one. And flea feasts on your pet's blood can lead to anemia and, in rare cases, death.

But fleas are not your pet's only nemesis. Tick bites can give your pet such infections as Lyme disease, ehrlichiosis, and Rocky Mountain spotted fever. And ticks can give those same infections to you.

The good news is fleas and ticks are getting easier to control. "In the last five years, flea products have greatly improved," says Ann Stohlman, V.M.D., a veterinarian at the Food and Drug Administration's Center for Veterinary Medicine. Some flea prevention treatments also help kill ticks.

In years past, veterinarians recommended getting rid of fleas by simultaneously "bombing" the house with insecticide, spraying the yard, and dipping the dog or cat, says Stohlman. Today, treating only the pet often takes care of the problem. "But if there is a severe flea infestation or if the problem persists, you may still need to treat the pet's environment," she says.


Photo by Beth Luddy

Consult your vet for the most appropriate flea and tick product to protect pets like "Bruce."

Types of Flea and Tick Products

Hundreds of pesticides, repellents, and growth inhibitors are approved or licensed to control fleas and ticks on cats and dogs or in their environment. (See "Pet Products to Control Pests"). Products range from oral medications that require a veterinarian's prescription to collars, sprays, dips, shampoos, and powders that are available at retail stores. "Spot-ons," liquid products applied directly to the pet's skin, often behind the neck, are among the latest weapons to be developed to fight fleas and ticks. Some products kill only ticks or adult fleas—others break the flea life cycle by preventing flea eggs from developing into adult fleas.

Some flea and tick products are not prescription drugs, yet are available only through veterinarians. "This is because the manufacturer chooses to sell its products through vets, so that the vet can provide important safety information to the client," says Elizabeth Luddy, D.V.M., an FDA veterinarian.

The Preventic collar is one such product. The collar kills ticks by interfering with a tick's ability to feed on dogs. It contains the insecticide amitraz, which paralyzes the tick's mouthparts. Amitraz should not be used on dogs that are sickly, pregnant, or nursing, or with certain drugs that may interact with the insecticide. The manufacturer, Virbac Corp., Fort Worth, Texas, sells the collar through veterinarians, who can ensure that a dog is healthy and can use the collar safely.

When to Treat

It's best to treat your pet at the beginning of flea and tick season,

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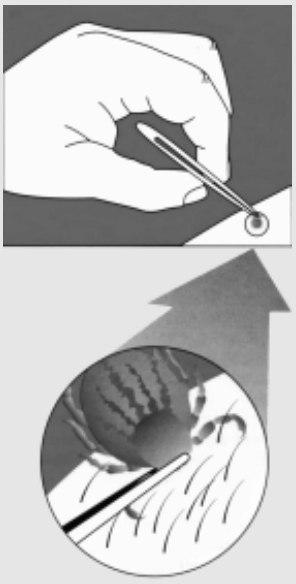
says Stohlman. The severity and length of the flea season vary depending on which part of the country you live in. "It can last four months in some places, but in other places, like Florida, fleas can live all year long," says Stohlman. Fleas also can live inside a warm house year-round.

In many areas, September is often the worst month for flea infestation. In most parts of the United States, the greatest chance of infection by a tick bite is May through September, the period of greatest tick activity by "nymphs." Nymphs are the stage of tick development that occurs after they have had their first blood meal and molt, and before they become adults.

How to Remove a Tick



If a tick is removed within 24 hours, the chances of it transmitting Lyme disease or other infections are much less. The illustrations (right) show how to remove a tick properly. Use fine-point tweezers to grasp the tick as close to the skin as possible. Pull gently. Avoid squeezing the body of the tick. Clean the site of the bite, your hands and the tweezers with disinfectant. You may want to wear protective gloves.

You also may want to place the tick in a small container, like a pill container, and bring it to your vet for identification. Never use a burned match, petroleum jelly, or nail polish to try to remove ticks. These methods are ineffective.

—L.B.

Lyme Disease

About 200 species of ticks live in the United States. Some of these can transmit infectious diseases, such as Lyme disease, to pets and humans. Studies indicate that dogs are 50 percent more susceptible to Lyme disease than humans, according to the American Veterinary Medical Association. Lyme disease is caused by a bacterium transmitted through the bite of the deer tick, also called the black-legged tick, which is no larger than the head of a pin.

Typical symptoms of Lyme disease in dogs include joint soreness and lameness, fever, and loss of appetite. Symptoms in humans include fatigue, chills and fever, headache, muscle and joint pain, swollen lymph nodes, and a red, circular skin rash.

Some of the products shown in "Pet Products to Control Pests" can control ticks on your pet. Many other tick repellents for pets and people are available in stores.

Read the Label, Talk to Your Vet

When buying a flea or tick product, it's important for pet owners to read the label and follow the directions carefully, says Steve Hansen, D.V.M., director of the ASPCA Animal Poison Control Center. Hansen reports a "serious problem" with the misuse of dog flea and tick control products containing the insecticide permethrin. Dogs can tolerate concentrated

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Photo by Joe Forman

Never use products on cats that are labeled for use on dogs only.

Using Flea and Tick Products Safely

- Read the label carefully before use. If you don't understand the wording, ask your veterinarian or call the manufacturer.
- Follow directions exactly. If the product is for dogs, don't use it on cats or other pets. If the label says use weekly, don't use it daily. If the product is for the house or yard, don't put it directly on your pet.
- After applying the product, wash your hands immediately with soap and water. Use protective gloves if possible.
- If your pet shows symptoms of illness after treatment, call your veterinarian. Symptoms of poisoning may include poor appetite, depression, vomiting, diarrhea, or excessive salivation.
- Store products away from food and out of children's reach.

—L.B.

permethrin, but "it can be lethal to cats," says Hansen. "Never use products on cats that are labeled for use on dogs only."

If the label states that the product is for animals of a certain age or older, don't use the product on pets that are younger, says Stohlman. Flea combs, which can pick up fleas, flea eggs, and ticks, may be useful on puppies and kittens that are too young for flea and tick products.

Talk to your vet about the flea and tick product most appropriate for your pet, Luddy advises. The product you use will depend on your pet's health and age, whether your pet is a cat or a dog, and whether it's an indoor or outdoor pet. Also check with your vet to determine whether the Lyme vaccine is right for your dog.

Rabbits, ferrets, and some other furry pets also can have flea and tick infestations. Reptiles, such as snakes, can get infections and anemia from tick bites. No flea or tick products are marketed specifically for use in these animals. Ask your veterinarian how to treat fleas and ticks in these and other exotic pets.

Linda Bren is a Writer-Editor with the FDA CONSUMER.

□

Pet Products to Control Pests

Hundreds of products are available to control fleas and ticks. Shown below are some of the most recently marketed products intended to treat pests on animals. If you are interested in tick control, call your veterinarian or the manufacturer to find out which kinds of ticks are found in your area and which products are effective against those ticks.

Product	*Administration*	*Species*	*Manufacturer*	*Pests Controlled*
*PROGRAM 6 MONTH INJECTABLE (lufenuron)	Injection	Cats	Novartis Animal Health 1-800-332-2761	Flea eggs
PROGRAM FLAVOR TABS (lufenuron)	Oral	Dogs and cats	Novartis Animal Health 1-800-332-2761	Flea eggs
*SENTINEL FLAVOR TABS (lufenuron + milbemycin oxime)	Oral	Dogs	Novartis Animal Health 1-800-332-2761	Flea eggs, heartworms, hookworms, roundworms, whipworms
ZODIAC FLEATROL FLEA CAPS (methoprene)	Oral	Dogs	Wellmark 1-800-950-4783	Flea eggs
ADVANCED CARE FLEA CONTROL CAPSULES (methoprene)	Oral	Dogs	Hartz Mountain 1-800-275-1414	Flea eggs
CAPSTAR (nitenpyram)	Oral	Dogs and cats	Novartis Animal Health 1-800-332-2761	Adult fleas
*REVOLUTION (selamectin)	Topical	Dogs and cats	Pfizer Animal Health 1-800-366-5288	*Dogs:* Adult fleas and eggs, heartworms, ear mites, sarcoptic mange, ticks *Cats:* Adult fleas and eggs, heartworms, ear mites, hookworms, roundworms
PREVENTIC COLLAR (amitraz)	Topical	Dogs	Virbac 1-800-338-3659	Ticks
ADVANTAGE (imidacloprid)	Topical	Dogs and cats	Bayer Animal Health 1-800-255-6826	Adult fleas
KILTIX (permethrin)	Topical	Dogs	Bayer Animal Health 1-800-255-6826	Ticks
FLEATROL POWER SPOT (permethrin + methoprene)	Topical	Dogs	Wellmark 1-800-950-4783	Adult fleas and eggs, ticks
FRONTLINE PLUS (fipronil + methoprene)	Topical	Dogs and cats	Merial 1-800-660-1842	Adult fleas and eggs, ticks

**Available by prescription only*

FDA APPROVES FIRST DRUG TO TREAT EPM

FDA has approved Marquis (ponazuril) the first drug to treat equine protozoal myeloencephalitis (EPM) in horses. EPM is caused by a parasite (*Sarcocystis neurona*) and is the most commonly diagnosed neurological condition in horses in America. EPM is widespread in North America, South America, and in Canada. In some areas of the United States, as much as 80-90% of the horse population may have been exposed to EPM. An estimated one percent of the horses exposed to the disease will develop clinical signs of EPM and require treatment.

The clinical signs of EPM may vary, and they may include weakness (particularly on one side), serious lack of coordination, and muscle wasting involving all four limbs. EPM is more prevalent in young (less than 5 years of age) and older horses (more than 13 years old). Diagnosis of EPM is difficult since there are at least four other central nervous system diseases which can closely resemble the disease.

FDA expedited the approval process for ponazuril because it was intended to reduce the suffering and death associated with EPM, and because there were no approved therapeutics for treating this devastating disease.

Ponazuril is supplied as an oral paste to be given once at day at the dose of 5 mg/kg for 28 days in adult horses. Bayer Animal Health, Shawnee Mission, Kansas, is the sponsor of the drug that will be available by prescription only from a licensed veterinarian. □

FDA SEEKING COMMENTS ON IMPORT TOLERANCES

The Food and Drug Administration (FDA) is soliciting comments on issues related to the implementation of the import tolerances provision of the Animal Drug Availability Act of 1996 (ADAA). The ADAA authorizes FDA to establish drug residue tolerances (import tolerances) for imported food products of animal origin for drugs that are used in other countries, but that are unapproved new animal drugs in the United States. Food products of animal origin that are in compliance with the import tolerances will not be considered adulterated under the Federal Food, Drug, and Cosmetic Act (the Act) and may be imported into the U.S.

In the August 10, 2001, *Federal Register* FDA published an advance notice of proposed rulemaking (ANPRM) on the import tolerance issue. FDA's Center for Veterinary Medicine (CVM) plans to hold a public advisory committee meeting on import tolerances on September 13-14, 2001. CVM intends to consider the comments made at the meeting and in response to this ANPRM in writing the proposed regulation.

Written or electronic comments on the ANPRM should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852, by December 10, 2001. Electronic comments should be submitted to *http://www.fda.gov/dockets/ecomments*. Comments should reference Docket No. 01N-0284.

Additional information on the ANPRM is included in the August 10, *Federal Register*, and from Frances Pell, Center for Veterinary Medicine (HFV-235), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-0188.

The Veterinary Medicine Advisory Committee (VMAC) meeting will be held on September 13-14, 2001, from 8:30 a.m. to 5:00 p.m. at the DoubleTree Hotel, Plaza Rooms I, II, and III, 1750 Rockville Pike, Rockville, MD. The VMAC will seek recommendations on the issue of import tolerances. The public comment period is planned for the afternoon of September 13 and the morning of September 14.

Information on the VMAC meeting is contained in the August 10, 2001 *Federal Register*, and from Aleta Sindelar, Center for Veterinary Medicine (HFV-3), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 301-827-4515. Information on the VMAC meeting is also available on the FDA Advisory Committee Information Line, 1-800-741-8138 (301-443-0572 in the Washington, DC area,) code 12546. □

STRICT PRISON SENTENCE GIVEN TO OWNER OF ILLEGAL DAIRY OPERATION

On July 9, 2001, the U.S. District Court for the Eastern District of California sentenced Arie C. Van Leeuwen to six months in jail and one year of supervised release for his repeated probation violations. Van Leeuwen, a Modesto, California, dairy owner, had been found guilty by the same court in April 2000 of violating a 1995 court injunction against his sale of livestock and of a felony count of introducing adulterated food into interstate commerce.

This injunction was ordered after he was found to have sold cattle containing illegal levels of antibiotic residues that might pose a significant public health risk. Such antibiotic residues are a public health risk because they may cause allergic reactions and changes in human intestinal microflora, which can trigger detrimental effects such as diarrhea, vitamin deficiencies, and complications with drug therapies. These changes can also contribute to the development and proliferation of antibiotic-resistant strains of disease-causing bacteria in humans who eat or handle meat bearing antibiotic residues.

Despite this court injunction, Van Leeuwen repeatedly sold livestock under fictitious names until he was charged and sentenced in April 2000 to a four-year term of probation including 12 months of home confinement,

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The following firms/individuals received warning letters for offering animals for slaughter that contained illegal drug residues:

- Michael L. Williams, President, Williams Cattle Co., Inc., London, KY
- J. Kenneth Fussell, Burns, TN
- Delmar Van Dam, Owner, High Desert Dairy, Lancaster, CA
- Maria Silveira, Owner, Silveira Dairy, Escalon, CA
- Richard A. Edwards, President, Oakland View Farms, Ridgely, MD
- John S. Leal, Adelino Ormonde, & Edward Ormonde, Partners, O & L Dairy #2, Tulare, CA
- Robert J. Sturm, Vice President, J-Rob Farms, Inc., Caledonia, NY

These violations involved illegal residues of penicillin, sulfamethazine, sulfadimethoxine, and sulfamethoxazole in dairy cows, and neomycin in calves.

Follow-up inspections revealed that Mr. Williams lacked controls to prevent the purchase and sale of animals adulterated with drug residues.

Mr. Fussell was found to be adulterating the drug Pfizer Pen BP-48, Sterile Penicillin G Benzathine and Penicillin G Procaine in aqueous suspension, because he was using the drug at higher than labeled dosages and without following labeled withdrawal times.

Mr. Van Dam was found to hold animals under improper conditions whereby diseased animals and/or medicated animals bearing potentially harmful drug residues are likely to enter the food supply.

Ms. Silveira was found to be adulterating the drug Mutual Pharmaceutical brand of sulfamethoxazole and trimethoprim tablets, since she did not follow her veterinarian's prescribed withdrawal time of thirty days prior to slaughter.

Mr. Edwards did not properly identify treated animals to assure they are not sold for slaughter, did not maintain treatment records, and he did not follow labeling directions for medicated feed.

O & L Dairy was found to lack an adequate system for determining the medication status of animals offered for slaughter, and for assuring that animals which had been medicated had been withheld from slaughter for the appropriate periods of time to deplete potentially hazardous residues of drugs.

Mr. Sturm was found to hold animals on his farm under conditions that are so inadequate that diseased animals and/or medicated animals bearing potentially harmful drug residues are likely to enter the food supply. In addition, he failed to use the drug, Albon, containing sulfadimethoxine, in conformance with the labeling.

A warning letter was issued to the following firms for violations related to 21 CFR Part 589.2000—Animal Proteins Prohibited in Ruminant Feed. This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy (BSE).

- Scott Nelson, Owner, Integra Fish Foods, Inc., Grand Junction, CO
- Bruce A. Burgett, General Manager, The Carrollton Farmers Exchange, Carrollton, OH

Violations included failure to label feeds that contain, or may contain, prohibited materials with the required cautionary statement "Do Not Feed to Cattle or Other Ruminants," insufficient customer records to track the distribution of products, and lack of written procedures for cleaning or flushing equipment after mixing feeds containing prohibited material.

Robert Kofkoff, President, Kofkoff Egg Farms, LLC, Bozrah, CT, received a warning letter for significant deviations from the Current Good Manufacturing Practice Regulations (GMP's). Mr. Kofkoff was cited for failure to conduct adequate clean-out procedures which could result in unsafe contamination of the finished product, and for the manufacture of a medicated feed for replacement chickens that is not approved for such use.

John C. Gale, Chief Executive Officer and Rajiv Lall, President, Vets Plus, Inc., Knapp, WI, received a warning letter for violations of GMP's in that products listed in their product catalogs are marketed with therapeutic claims and without proper approvals. These products include AGRI PLUS Calcium Drench, Vets Plus Cal-C-Fresh, AGRI PLUS CMPK with D3 Drench, Vets Plus Keto-Nia Fresh, and HORSES Prefer BIO-HOOF. □

STRICT PRISON SENTENCE GIVEN TO OWNER OF ILLEGAL DAIRY OPERATION (Continued)

financial penalties, and prohibitions from the sale or transportation of cattle for slaughter.

Nevertheless, Van Leeuwen continually violated the terms of this sentence through early 2001 leading his probation officer to file a petition with the Court. Four charges were cited:

1. the failure to obey all laws;
2. the failure to submit mandated monthly report forms;
3. the failure to comply with home confinement conditions; and
4. the transportation of animals to cattle auction.

Taking into consideration Van Leeuwen's previous conduct, the Court sentenced him to six months in prison followed by a year of supervised release that includes mandatory attendance in dairy management classes. □

CONSENT DECREE SIGNED IN TISSUE RESIDUE CASE AGAINST CALIFORNIA DAIRIES

On July 30, 2001, the U.S. District Court for the Eastern District of California accepted and entered a Consent Decree of Permanent Injunction between the United States, and Joe Sozinho Sr., Danny Sozinho, and Dimas M. Sozinho. These individuals were doing business as Joe Sozinho Dairy #1 and Joe Sozinho Dairy #2 in Hanford, California. The Dairy #1 milks approximately 650 dairy cows daily, which yields approximately 5,500 gallons of fluid milk per day. The Dairy #2 milks approximately 450 dairy cows daily, which yields approximately 2,800 gallons of fluid milk per day.

FDA's San Francisco District (FDA/SAN-DO) conducted six inspections from 1994 through December 2000 in response to several violative drug residues in edible tissues of both dairies reported by the U.S. Department of Agriculture's Food Safety and Inspection Service (USDA/FSIS). Based on these inspections, FDA issued two Warning Letters to this firm. Despite the warnings given to the Sozinho's during these FDA inspections, as well as several residue violation notification letters issued by the USDA/FSIS to them for illegal tissue residues detected in their animals, they failed to take adequate corrective actions. Voluntary approaches were not successful in correcting the severe animal husbandry and drug adulteration problems found at both dairies.


Photo by Karen Kandra

Cattle sold containing illegal drug residues pose a significant public health risk.

The Consent Decree permanently restrains and enjoins the Sozinho's from selling cattle for human food consumption until all of the provisions of the Decree are met. The provisions of the Decree include an animal identification system, a medication record keeping system, a drug inventory system, a drug use system, a quarantine system, and an animal sales certification system. In addition, the Sozinho's reimbursed FDA's costs in the amount of $12,314.38 for investigational expenses incurred subsequent to the 1994 inspection and Warning Letter. FDA/SAN-DO will periodically monitor both dairies.

FDA/SAN-DO conducted all the investigative work for this case. CVM's Division of Compliance, FDA's Office of the Chief Counsel and the U.S. Department of Justice's Office of Consumer Litigation handled the case processing, litigation, and negotiation. □

Note from the editor: The following three articles are abstracts from posters presented by the staff of CVM's Office of Research/Division of Animal and Food Microbiology at the 101st Annual Meeting of American Society for Microbiology, Orlando, FL, May 20 - 24, 2001.

CHARACTERIZATION OF CHLORAMPHENICOL RESISTANCE IN *ESCHERICHIA COLI* ASSOCIATED WITH DIARRHEA IN NEONATAL SWINE

by K. M. Bischoff, D. G. White, P. F. McDermott, S. Zhao, J. J. Maurer, and D. J. Nisbet

Summary

We have characterized the antimicrobial susceptibility patterns of 91 isolates of *Escherichia coli* associated with diarrhea in neonatal pigs from multiple farms in Oklahoma. Minimum inhibitory concentrations were determined for 17 antimicrobials that are monitored by the National Antimicrobial Resistance Monitoring System. Based on resistance breakpoints determined by the National Committee for Clinical Laboratory Standards, 88 of 91 isolates (97%) were resistant to at least one antibiotic and 81 of 91 (89%) were resistant to four or more antibiotics. The broad-spectrum antibiotic chloramphenicol (CML) has been removed from use in food animals since 1985, yet we observed CML resistance in 47/91 (52%) of these isolates. The *cmlA* gene, which encodes a CML efflux pump, was detected by polymerase chain reaction in 46 of the CML resistant isolates, and 4 of these also possessed the *cat2* gene encoding a chloramphenicol acetyltransferase. The one CML resistant isolate that did not contain either *cmlA* or *cat2* did, however, possess the *flo* gene, which encodes an efflux pump that confers resistance to both florfenicol and CML. The genetic relatedness of all 91 isolates was assayed by ribotyping. Seventeen distinct ribogroups were identified but 72% of the isolates clustered into 6 major ribogroups. CML resistance was found in all but one of the major ribogroups, the largest containing 31 isolates with 23/31 resistant to CML. Our data suggests that the *cmlA* resistance genotype is widely disseminated in enterotoxigenic *E. coli* isolated from swine, and that the chloramphenicol resistance phenotype persists even in the absence of CML selection pressure.

□

IDENTIFICATION AND EXPRESSION OF CEPHAMYCINASE *BLA*$_{CMY}$ GENES IN *ESCHERICHIA COLI* AND *SALMONELLA* ISOLATED FROM FOOD ANIMALS AND GROUND MEATS

by S. Zhao, D. G. White, P. F. McDermott, S. Friedman, L. English, S. Ayers, J. Meng, J. J. Maurer, R. Holland, and R. D. Walker

Summary

The emergence of bacterial resistance to antimicrobial agents is a worldwide problem that has been associated with inappropriate use of these agents in human and veterinary medicine. Recently, plasmid-mediated b-lactamases with extended resistance spectra, such as cephamycinase (CMY), have emerged. In this study, 60 *E. coli* and 21 *Salmonella* isolates, recovered from diseased cattle, poultry, swine and retail meats, that exhibited decreased susceptibilities to ceftiofur and/or ceftriaxone were examined for the presence of bla_{CMY} genes using a PCR assay. PCR analysis revealed that 54 (90%) of the *E. coli* isolates and all 21 *Salmonella* possessed a bla_{CMY} gene. DNA sequence analysis of nine bla_{CMY} PCR products (four from *E. coli* and five from *Salmonella*) indicated 95 to 99% homology to previously reported bla_{CMY-2} genes found in *Klebsiella pneumonia* and *Salmonella* Seftenberg. The bla_{CMY} gene from an *E. coli* strain isolated from retail chicken meat was successfully transferred via conjugation. Transconjugants demonstrated resistance to six b-lactams drugs tested, including ceftiofur, ceftriaxone, cefoxitin, cephalothin, ampicillin and amoxicillin/clavulanic acid. This bla_{CMY} gene was subsequently cloned into expression vector pET34b+ and transformed into *E. coli* BL21(DE3)pLysS. The transformant displayed resistance to ceftiofur, cepholothin, ampicillin and amoxicillin/clavulanic acid, and decreased susceptibilities to ceftriaxone, and cefoxitin. The cloned *E. coli* bla_{CMY} gene sequence was 100% homologous to a previously reported bla_{CMY-4} gene of an *E. coli* strain isolated from leukemia patients. Our results indicate that bla_{CMY} genes are commonly present in ceftiofur- and/or ceftriaxone-resistant *E. coli* and *Salmonella* of animal and food origin, and that this plasmid-mediated resistance is transferable via conjugation.

□

ESCHERICHIA COLI O157:H7 MARR: GENETIC ANALYSIS OF ITS ROLE IN GROWTH IN THE PRESENCE AND ABSENCE OF ANTIBIOTICS

by S. Yaron, S. Golding, D. G. White, and K. R. Matthews

Summary

The *marRAB* operon is a regulatory locus that controls multiple drug resistance in gram negative bacteria such as *Escherichia coli* and *Salmonella* by altering the expression of many chromosomal genes. MarR, a member of phenolic-binding regulatory proteins is the transcriptional repressor of the operon. A mutation within the *marR* gene in *E. coli* K-12 leads to constitutive transcriptional activation of *marRAB*, resulting in decreased influx and increased efflux of toxic agents. *marR* from the foodborne pathogen *E. coli* O157:H7 has been amplified by PCR. Its sequence is 98% identical to MarR from *E. coli* K-12. Upon exposure of *E. coli* O157:H7 to chloramphenicol (Cm) we isolated a mutant that does not express MarR. This mutant grew on higher concentrations of tetracycline (2.5 mg/ml), nalidixic acid (4 mg/ml) and ciprofloxacin (0.025 mg/ml) compared to the parent strain.

The role of MarR in growth was analyzed. We compared the growth of MarR mutant to the parent strain, in the presence and absence of Cm (7 mg/ml), under various conditions. No significant differences were observed in growth curves of the parent and the mutant in the conditions examined (rich and minimal media, acidic conditions and at a temperature range of 24-42°C). Those results demonstrate that under standard growth conditions the multiple antibiotic resistant mutant is highly competitive with the susceptible parent.

Conditions required for induction of antibiotic resistance of MarR mutant were examined. The mutant grew at 30°C and below on rich media supplemented with Cm, but growth was slow at 37°C, and no growth occurred above 37°C. No growth occurred in minimal broth supplemented with Cm. MarR mutant was pre-conditioned by culturing for 17 h in Luria broth containing Cm. Significantly greater resistance was observed with the pre-conditioned mutant. In general, regardless of antibiotic, growth rates were greater and lag periods shorter for the preconditioned mutant. Results support the hypothesis of amplifiable multiple antibiotic resistance.

□

LETTER TO THE EDITOR

FDA's Center for Veterinary Medicine (CVM) has received a letter concerning a sentence in an article entitled "Antibiotic Resistance from Down on the Farm" that appeared in the January/February 2001 issue of the ***FDA Veterinarian****. (This article had been reprinted from the January/February 2001* ***FDA Consumer*** *magazine.) Following are excerpts from the letter sent to CVM by Charles L. Hofacre, D.V.M., M.A.M., Ph.D., President of the American Association of Avian Pathologists (AAAP).*

Dear Dr. Sundlof:

The American Association of Avian Pathologists (AAAP) is the professional organization of those veterinarians and scientists with an interest in diseases of avian species. As such, our membership includes the vast majority of those veterinarians responsible for the health management and antibiotic treatment of U.S. poultry, as well as those with academic interests in avian diseases. We are acutely interested in the responsible use of antimicrobials in poultry, as evidenced by our representative's participation in the Steering Committee on Antibiotic Resistance. This participation resulted in the rapid development and dissemination of the "Guidelines for Judicious Therapeutic Use of Antimicrobials in Poultry," which basically articulated the current standard of practice in the poultry industry.

Consequently, we are distressed to note that page 2 of (the January-February 2001 *FDA Veterinarian*) contains the article "Antibiotic Resistance from Down on the Farm" . . . which contains the statement, "But the size of flocks precludes testing and treating individual chickens—so when a veterinarian diagnoses an infected bird, the farmers treat the whole flock by adding the drug to its drinking water." In practice, poultry veterinarians assemble information on a representative sampling of the house or flock, and then determine an economically viable course of action. The requirement for an economically viable course of action precludes use of antibiotics based on pathology in a single bird. In other words, flocks of birds are treated only when a significant number of birds are either clinically affected or are showing early signs of disease (i.e., ruffled feathers, nasal/ocular discharge, etc.), thus preventing the rapid spread of the disease from one individual to the next until the entire flock becomes infected . . . .

Dr. Sundlof has responded to Dr. Hofacre's concerns as follows:

Dear Dr. Hofacre:

Thank you for sharing your comments about the article "Antibiotic Resistance from Down on the Farm" that was included in the January/February 2001 *FDA Veterinarian*. As you point out, the article does not accurately portray the proper approach veterinarians use under the Judicious Use Principles to diagnose poultry flocks before treatment with an antimicrobial.

We at FDA/CVM support the work of veterinarians to reduce the risk of antimicrobial resistance from food of animal origin. Just like the members of AAAP, we in FDA/CVM support the American Veterinary Medical Association's development of the Judicious Use Principles. In fact, CVM has sponsored the development and distribution of educational material concerning the Judicious Use Principles. We want to continue our partnership with your organization, with others representing veterinarians, and with all of our stakeholders so that we can jointly develop the best approach to the issue of antimicrobial resistance, an approach that helps us to ensure food safety and that helps you have the best products possible to properly treat the animals in your care.

Sincerely yours,
Stephen F. Sundlof, D.V.M., Ph.D.
Director, Center for Veterinary Medicine

NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Fort Dodge Animal Health Division of American Home Products Corp. (NADA 141-189)	Moxidectin (ProHeart® 6) Rx	Dogs. For prevention of heartworm disease and treatment of existing hookworm infections	**SUBCUTANEOUS**—The NADA provides for the injection of a constituted, sustained-release suspension for prevention of heartworm disease caused by *Dirofilaria immitis* and for treatment of existing larval and adult hookworm (*Ancylostoma caninum*) infections. *Federal Register* 07/09/01

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ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Blue Ridge Pharmaceuticals, Inc. (ANADA 200-302)	Ivermectin, Pyrantel Pamoate (Iverhart™ Plus) Rx	Dogs. For the prevention of heartworm disease and for treatment and control of certain gastrointestinal parasites.	**ORAL**—The Iverhart Plus flavored chewables in the ANADA are a Generic copy of Merial's Heartgard® Plus Chewables, NADA 140-971. *Federal Register* 07/09/01
Pennfield Oil Co. (ANADA 200-295)	Chlortetracycline Soluble Powder (Pennchlor™ 64)	Cattle, swine, chickens, turkeys. For the control and treatment of various bacterial diseases.	**ORAL**—The Pennchlor 64 soluble powder in the ANADA is a generic copy of American Cyanamid's Aureomycin Soluble Powder, NADA 65-440. *Federal Register* 07/10/01

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SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Pharmacia and Upjohn Co. (NADA 140-338)	Ceftiofur (Naxcel) Rx	Cattle. For the treatment of several bacterial diseases.	**INTRAMUSCULAR AND SUBCUTANEOUS**—The supplemental NADA is to add the subcutaneous route of administration. *Federal Register* 06/15/01
Merial Ltd. (NADA 136-742)	Clorsulon (Curatrem® drench)	Cattle. For the treatment of liver fluke infestations.	**TOPICAL**—The supplemental NADA provides for establishing a tolerance of 0.1 part per million of clorsulon as residue in muscle tissue. The Acceptable Daily Intake (ADI) for total residues of clorsulon is 8 micrograms per kilogram of body weight per day. *Federal Register* 07/06/01

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