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BSE Cow in U.S. Triggers FDA, USDA Cooperative Response, New Rules Announced

by Jon F. Scheid, Editor

As soon as the U.S. authorities announced on December 23 that a cow in Washington State apparently was infected with Bovine Spongiform Encephalopathy (BSE), the first case in the U.S., officials from the Food and Drug Administration immediately joined with those from the U.S. Department of Agriculture to implement existing and pretested response plans. Many officials gave up most of their intended Christmas and New Year's holidays. But through their work, meat from the infected cow was traced and recalled, and more importantly, the potentially infectious material from the cow was stopped from further distribution, and kept out of the food and feed supply.

Here is an overview of the events that started when the presumptive positive cow was first discovered, and a description of the responsibilities and functions of FDA and USDA—how they work together to ensure the safety of public health.

FDA

USDA and FDA have separate roles that, together, were able to protect consumers and the U.S. cattle herd. While USDA went to work to track down the source herd of the infected animal and to recall meat that could have come from the animal, FDA's primary responsibility was to be sure the disease didn't spread via feed.

Scientists believe that BSE is transmitted from animal to animal only through feed containing infectious material. Scientists believe that protein in rendered products made from an infected cow can contain the infectious agent. Therefore, the underlying principal of the BSE feed rule FDA implemented in 1997 is that ingredients that could carry the infectious agent cannot be fed to cattle or other ruminants.

After the BSE-infected cow was discovered, FDA immediately sent investigators to any facility that might have handled the byproducts made from the infected animal, working cooperatively with rendering companies. Ultimately, FDA inspected and traced products related to the BSE positive cow at 22 facilities, including feed mills, farms, dairy farms, calf feeder lots, slaughter houses, meat processors, transfer stations, and shipping terminals.

The investigators were able to track all rendered products—approximately 2,000 tons—that could contain material from the infected cow. None of it was used in feed.

One factor aiding the investigation was that all of the facilities that handled the byproduct were in compliance with FDA's 1997 BSE feed rule. Dr. Stephen Sundlof, Director of the FDA's Center for Veterinary Medicine, said during a December 26 technical briefing for the press about the BSE case, "We inspect all facilities that handle ruminant protein on a yearly basis, and currently all of the firms that are located in Washington State are in compliance."

Implementation of the BSE Rule

When FDA implemented the BSE feed rule in 1997, the first step for the Agency was an education campaign, followed up with inspection and enforcement activities.

FDA has provided nationwide educational seminars on the feed rule, developed a CD-ROM for training, held teleconferences, developed guidances for different segments of the animal feed industry and for State and Federal inspectors, and published a variety of articles. In addition, FDA has met with industry trade groups to discuss coordination of educational efforts with affected parties. CVM has made its compliance program guidance, which describes the inspection process for Federal and State inspectors, available on its website so the rules and the tools FDA will use to enforce them are readily available.

FDA and States have identified all the feed mills, renderers and other firms that handle material that is prohibited from cattle feed under the BSE rule (so-called "prohibited material"). These firms will

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Compliance Rate for BSE Feed Rule Tops 99%

According to information from the BSE inspection database available on FDA's website, more than 99% of all firms that handle material prohibited from cattle rations are in compliance with the rule. Here are the statistics:

- **Total inspections reported by FDA and States (as of 1/23/04)** 26,000
  (About 70% of the inspections were conducted by State officials. FDA officials did the rest.)
- **A total of firms inspected (as of 1/23/04)** 13,672
- **Total of firms handling prohibited material (as of 1/23/04)** 1,949
- **Total firms with significant violation of BSE rule (as of 1/23/04)** 5

be subject to inspection at least once a year, and more often if violations of the rule are found. These firms are most critical to feed safety because they are the first to handle feed that can carry the BSE infectious agent.

When FDA finds a firm with a significant violation, it assigns the firm a status of "Official Action Indicated," which means that the firm must quickly address the violations and it will be subject to a prompt follow-up inspection.

Depending on the nature of the violation, a firm's products could be recalled, it could receive an FDA warning letter (which demands a response from the firm about how it will correct the violations), or it could find itself in court and facing a possible injunction.

From 1997 to the end of 2003, 47 firms had recalled a total of 280 products. 12 of the recalls occurred during 2003. Also, FDA has issued 63 warning letters. And the court has ordered one permanent injunction against a feed company.

The inspection and enforcement activity has resulted in a compliance rate greater than 99%.

New Rules

On January 26, Health and Human Services Secretary Tommy Thompson announced four changes that will be made to the BSE feed rule that are designed to further tighten the restrictions to prevent BSE's spread.

1. Mammalian blood and blood products will be prohibited from feed for ruminants. The previous exemption for pure porcine or equine products still exists, so porcine and equine blood meal collected at single species slaughter operations and processed using dedicated equipment can still be fed to ruminants.
2. Poultry litter will be prohibited from ruminant feed. The major concern is that poultry feed containing prohibited material can spill into the litter, and then be consumed by cattle. Poultry litter is made of bedding, spilled feed, feathers, and fecal matter collected in poultry houses.
3. Plate waste will be prohibited. Plate waste is excess meat that was prepared for human consumption, collected from restaurants and processed into a feed ingredient. Currently, inspectors have no way to determine whether processed meat in feeds came from plate waste or other sources. By eliminating this exemption, enforcement of the rule will be more effective.
4. Feed production facilities must have separate equipment, facilities or production lines if they use prohibited protein for manufacturing feed for non-ruminant animals and also make feed for ruminants. This rule change will prevent cross-contamination of feed during processing.

Along with the new measures, FDA announced that it would boost inspections.

FDA itself intends to conduct 2,800 inspections, and States will conduct 3,100 contract inspections during 2004. States will also report on 700 additional inspections. FDA will be sure that 100% of all known renderers and feed mills that handle prohibited material are inspected.

Other Measures

FDA announced other changes concerning consumer products.

FDA will prohibit the use of material made from "downer" (cattle unable to walk) or dead cattle in any FDA-regulated human food, including dietary supplements, and cosmetics.

Specified risk material, which is the material most likely to contain the BSE infectious agent and is made up of cattle brain, skull, eyes, or spinal cord of animals 30 months or older, and a portion of the small intestines and the tonsils of all cattle, regardless of age, will be prohibited from FDA regulated food and consumer products.

Also, mechanically separated beef, which comes from a process designed to remove bits of meat from bones, will be prohibited from FDA products, because it may contain specified risk material.

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FDA VETERINARIAN

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BSE Cow in U.S. Triggers Cooperative Response *(Continued)*

USDA

The two agencies within USDA most directly involved with the response to the discovery of a BSE-infected cow in Washington State are the Animal and Plant Health Inspection Service (APHIS), which has responsibility for animal disease surveillance, and the Food Safety and Inspection Service (FSIS), which has the responsibility for ensuring the foods USDA regulates are safe.

Under USDA's response plan, implemented in 1996, APHIS personnel conduct routine surveillance on cattle coming to slaughter as well as take samples from animals that display signs of central nervous system disorder at slaughter. Samples are sent to the USDA's National Veterinary Services Laboratory in Ames, Iowa. Any positive finding at that laboratory is considered a "presumptive positive," and samples are sent to the United Kingdom's Central Veterinary Laboratory, which is also known as the world reference laboratory, for confirmation.

The BSE positive cow was sampled as part of the routine sampling procedures. It was a "downer," believed to be suffering from the after effects of a difficult calf delivery. The sample was put in the routine queue for testing at the laboratory in Ames. The infected cow was slaughtered December 9. The sample arrived at the Ames laboratory on December 11. The first positive test result was found on December 22. The laboratory did confirmatory tests on December 23, which also indicated that the cow was positive. Later that day, Agriculture Secretary Ann Veneman announced the "presumptive positive" finding.

The "presumptive positive" was confirmed on December 25 by the world reference laboratory in Weybridge, England.

With the finding of a positive cow, APHIS began a search for the birth herd of the infected cow and for any other animals that might have become infected with BSE.

FDA BSE Response Plan

FDA has an overall BSE emergency response plan that coordinates with other Federal agencies, especially USDA. Each Center within FDA has part of the overall FDA plan. CVM's part of the plan focuses on communication and coordination with other agencies (Federal, State, and local) and with regulated industry.

FDA and CVM had tested their plans several times before the Washington State incident, so the plans would be free of glitches. When the incident occurred, FDA's and CVM's response plans worked well.

Once the BSE-positive cow was discovered, FDA's BSE response plan called for the Agency to immediately establish an Emergency Operations Center that served as a single point of contact for FDA's response. The center maintained contact with the Office of the Secretary of the Department of Health and Human Services, with USDA's APHIS and FSIS agencies, and with other emergency centers as appropriate.

Also as part of FDA's emergency plan, FDA dispatched inspection teams to locate the byproducts that could have been made from the infected cow to make sure the material was not used in feed. The investigating teams were sent from FDA's Seattle District Office. The investigators successfully tracked down all byproducts that could carry the infectious agent, keeping the byproducts from entering the feed supply.

BSE does not spread among animals by contact. Instead, the infectious agent is spread only through feed, scientists believe. So APHIS was looking for animals from the birth herd and other herds the infected animal had been in, because the animals from those herds could have been infected by consuming the same feed that infected the Washington State animal.

APHIS's epidemiological work progressed rapidly. Four days after Agriculture Secretary Veneman first announced the discovery of the infected animal, USDA had initial evidence to suggest that the animal came from Canada. Shortly after that, USDA discovered that the animal, born in April 1997, was older than the feed ban, which was begun in the U.S. and Canada in late 1997. The cow most likely received the infectious feed before the ban was implemented.

APHIS concentrated its epidemiological investigation on 81 cows imported to the U.S. from a dairy herd in Alberta, Canada, in 2001. Officials were able to trace a significant number of those animals and their offspring. Several were sacrificed and tested for BSE. All were found to be negative.

Meanwhile, FSIS began a "Class II" recall of meat that was produced at the slaughter plant the same day the infected cow was slaughtered. FSIS recalled 10,418 lbs. of meat distributed in Western and Northwestern states. FSIS did not believe the meat was unsafe, and the recall was done as a precaution, according to Dr. Ron DeHaven, USDA's Chief Veterinary Officer. "It's important to recognize that meat represents a minuscule risk, and it's only being recalled out of an abundance of caution," he said during a technical briefing of reporters on December 27, 2003.

Also, as part of USDA's response plan, the Department held technical briefings almost daily during the first two weeks following the discovery of the BSE-positive cow. At the briefings, technical experts explained recent developments and answered reporters' questions.

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BSE Cow in U.S. Triggers Cooperative Response *(Continued)*

BSE in the U.S. – TIMELINE OF SIGNIFICANT EVENTS

December 9, 2003

Following standard protocols, USDA took samples from a Holstein cow, slaughtered at Verns Moses Lake Meats, Moses Lake, Washington, to test for BSE. The cow was a downer (non-ambulatory), but she had shortly before suffered complications from giving birth, and her difficulties walking were thought to stem from that. The samples were sent to USDA's National Veterinary Service Laboratories, Ames, Iowa. Because the animal had no signs of neurological disease at slaughter, the samples were not given high priority for BSE sampling

December 22, 2003

Preliminary tests at USDA's laboratory were positive for BSE, and the laboratory started further testing.

December 23, 2003

USDA's lab used the internationally recognized "gold standard" test on the samples, and confirmed the earlier positive finding. Agriculture Secretary Ann Veneman in a press conference announced the "presumptive positive" result for BSE—the first case of BSE in the U.S. USDA immediately began traceback measures to find the meat from the BSE-suspect animal and initiatived a "Class II" recall of the meat from the entire day's slaughter at Verns Moses Lake Meats for the day the BSE-suspect cow was slaughtered. 20 animals had been slaughtered that day. The recall was for 10,410 lbs. of meat.

USDA also begins to trace of all animals that could have been infected at the same time as the cow in Washington State.

December 24, 2003

FDA announced that it had dispatched several teams of investigators to find any FDA-regulated products that were or could have been made from the infected cow, including animal feed.

December 25, 2003

The world reference laboratory in Weybridge, England, confirmed that the cow was infected with BSE.

December 27, 2003

USDA announced that the infected cow was mostly likely imported from Canada, and was probably born in April 1997, which was before the BSE feed rules were implemented in the U.S. and Canada.

FDA announced that all the potentially infectious material that could have gone into feed was found before any of it was used to manufacture feed. An estimated 2,000 tons of material was traced and kept out of feed.

December 30, 2003

USDA Food Safety and Inspection Service announced a series of rule changes designed to keep suspected BSE animals out of the food chain. The rules included a ban on the use of downer animals and specified risk material.

December 31, 2003

FDA announced that it fully supports the safety policies announced by USDA.

January 6, 2004

USDA announced that DNA evidence proves that the BSE-infected animal came from a dairy farm in Alberta, Canada.

January 26, 2004

The U.S. Department of Health and Human Services announced measures it is taking to increase safeguards against BSE in the U.S., including changes to the 1997 BSE feed rule and restrictions on the use of material of bovine sources that could be used in products for human consumption.

(Main narrative continued, next page)

President's Fiscal Year 2005 Budget Would Increase BSE Funding $8 Million

The President's proposed budget for fiscal year 2005, released February 2, would boost spending to prevent Bovine Spongiform Encephalopathy by $8,325,000 to support new Food and Drug Administration and U.S. Department of Agriculture safeguards against BSE.

With this increase, total spending on BSE control is increased to $29.8 million, which includes the $21.5 million in the base budget.

The FDA and USDA initiatives were adopted following the December 23, 2003, discovery of an infected cow in the U.S. imported from Canada.

The requested resources will enable FDA to

- Carry out (by FDA) an additional 920 risk-based BSE inspections and 600 targeted sample collections and analyses of both domestic and imported animal feed or feed components;
- Fund 2,500 more State inspections of animal feed firms;
- Acquire further information on feed firms and firms handling prohibited rendering materials; and
- Strengthen the States' infrastructures to monitor, and respond to, potential feed contamination with prohibited materials.

BSE Cow in U.S. Triggers Cooperative Response *(Continued)*

USDA rule changes

In response to the discovery of the BSE-infected cow, USDA on December 30, 2003, announced changes to its rules on meat.

- Meat from downer cattle would no longer be permitted in human food.
- Product from cattle tested for BSE would have to be held until tests confirmed that the cattle did not have BSE.
- Specified risk materials, which include skull, brain, trigeminal ganglia, eyes, vertebral column, spinal cord and dorsal root ganglia of cattle over 30 months of age and the small intestine of cattle of all ages, would no longer be allowed to enter the food supply.
- Material that could carry BSE infectivity could not be used in the process called "Advanced Meat Recovery," which is an industrial technology that removes muscle tissue from bone and beef carcasses under high pressure.
- Air-injection stunning, a process used in the slaughter plant, would no longer be allowed.
- Mechanically separated beef would no longer be allowed in human food.

BSE and the Safety of Pets

The same safeguards in place to protect the U.S. food supply from the agent that causes Bovine Spongiform Encephalopathy (BSE) are also protecting pet foods.

Shortly after government officials first announced that a cow in the U.S. had tested positive for BSE, pet owners began contacting the Center for Veterinary Medicine to ask if their pets would be safe. In response, CVM issued this statement:

"With the exception of cats, no pets (companion animals) are known to be susceptible to the infectious agent that causes BSE in cattle. No evidence of BSE has ever been found in dogs, horses, birds, or reptiles.

"However, cats are susceptible. Approximately 90 cats in the UK and several cats in other European countries have been diagnosed with the feline version of BSE, or FSE. Before it was recognized that they were susceptible to the BSE agent, cats were exposed to the infectious agent through commercial cat food or through meat scraps provided by butchers. The number of reported cases of FSE in the UK and Europe has been declining annually since 1994 after implementation of feed bans in those countries.

"Currently in the U.S., animal products that are prohibited from cattle feed are acceptable for use in pet food. Such products include meat and bone meal, for example. However, FDA believes that the safeguards it has put into place (specifically, the 1997 rule banning the use of mammalian tissue in ruminant feeds) to prevent BSE in the U.S. have also protected cats. To date, no case of FSE has been found in the U.S.

"Material from the BSE positive cow in Washington State (discovered December 23, 2003) did not pose a risk to cats in the U.S. because none of it was released into distribution. All firms involved with the incident in Washington State were found to be in compliance with the BSE rules.

"In addition, when the BSE positive cow was found in Canada in May 2003, the FDA stopped imports of all pet foods made from material derived from mammalian sources, and the pet food manufacturer recalled the food it had manufactured that was thought to contain material from the infected cow."

FDA continues to review these safeguards to be sure they are adequate, especially in light of the first BSE case found in the U.S. FDA announced additional measures on January 26 to further safeguard the U.S. food supply against BSE. These actions will diminish the risks of BSE's spread even further, thus better protecting all pets.

International Activities

FDA Hosts International BSE Discussions

The Food and Drug Administration, particularly individuals of the Center for Veterinary Medicine, met and had discussions with government and industry officials from a number of countries during January and early February concerning the implications of the first case of Bovine Spongiform Encephalopathy (BSE) found in the U.S.

The foreign representatives wanted to know what FDA and CVM are doing to be sure that animal feed and other FDA-regulated products that have the potential to contain the BSE agent are appropriately safeguarded. These countries import a number of products from the U.S., and continued trade depends on how FDA and the U.S. Department of Agriculture are controlling BSE risk. CVM is treating these meetings and other related correspondence from foreign regulators with the highest priority.

Officials came from Japan, Canada, Mexico, and some of the countries of Central America, South America, and the Caribbean to meet with FDA officials. FDA officials, in cooperation with USDA officials, also met with several agricultural attachés from Washington, D.C.-based embassies in January to discuss BSE.

FDA officials from CVM, Center for Food Safety and Applied Nutrition (CFSAN), and Office of International Programs (OIP) met on January 8 with officials from Japan's Ministry of Agriculture, Forestry, and Fisheries, from Japan's Ministry of Health, Labor, and Welfare, and from Japan's Food Safety Commission. The representatives discussed BSE control measures in animal feed and food additives.

On January 13, CVM, CFSAN, and OIP representatives met in separate meetings with officials from the Canadian Food Inspection Agency (CFIA) and from Mexico's Secretaría de Agricultura, Ganadería, Desarrollo Rural, Pesca y Alimentación (SAGARPA) to discuss current feed safety measures to control BSE in the U.S.

Both the Canadian and Mexican delegations expressed a strong desire to coordinate changes in Canada with any changes that FDA may make in its feed ban, as these countries are also considering such changes in their national requirements.

CVM representatives met with representatives of the Mexican feed, food, and animal industries on January 26 at USDA to discuss CVM measures to control BSE in animal feeds.

CVM and OIP representatives also met at USDA on January 12 with a large number of agricultural attachés based in the foreign embassies in Washington, D.C., to discuss CVM's measures to control BSE in animal feeds. On January 31, CVM met with the EU agricultural attachés at the Irish Embassy to discuss the latest BSE control measures being taken by CVM, including those measures publicly announced on January 26.

On February 4, CVM met with the Chief Veterinary Officers of a number of countries from the regions of Central America, South America, and the Caribbean to learn more about FDA's latest initiatives to assure the safety of animal feeds with regard to the risk from BSE.

New Editor

The Center for Veterinary Medicine has named Jon Scheid as editor of *FDA Veterinarian*, replacing Karen Kandra, who retired from government service on January 2, 2004.

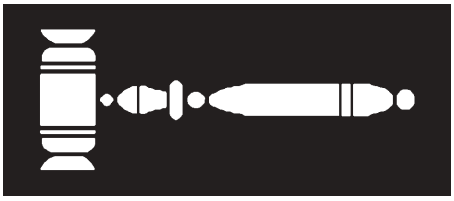
Mr. Scheid has been with the Center for more than six years, working in the communications area. For CVM, he has worked with trade press reporters, and drafted articles and information pieces. In addition, he has experience in the private sector publishing industry.

The Center currently has no plans to change the mix of articles and other information you've been finding in *FDA Veterinarian*. The publication is meant to give you information about Center initiatives and accomplishments, as well as tell you about the people who make up CVM.

If you have suggestions on features or types of information you would like to see in *FDA Veterinarian*, or if you have a comment about it, please contact Mr. Scheid by phone at 301-827-3797, by e-mail at jon.scheid@fda.gov, or by mail at HFV-3, 7519 Standish Place, Rockville, MD 20855, attn: *FDA Veterinarian*.

Regulatory Activities

by Linda A. Grassie, Director, Communications Staff



The following firms/individuals received Warning Letters for offering animals for slaughter that contained illegal residues:

- Fred M. Cox, Jr., Owner, Fred M. Cox, Jr. Farm, Talala, OK
- Tom Osterkamp, Owner, Osterkamp Dairy, Corona, CA
- Frank N. Konyn, Partner, Frank Konyn Dairy, Escondido, CA
- Hans N. Nederend, Owner, Mirada Dairy, Homedale, ID
- Jacobus L. De Groot, Partner and John De Groot, Partner, Visalia, CA
- Henry J. te Velde, D.V.M., President, JVJ Dairy, Inc., AKA Meadow Dairy, Winton, CA
- Henry C. Hafliger, Owner, Desert Rose Farms, Filer, ID
- Daniel E. Dallmann, President, Dallmann Farms, Inc., Brillion, WI
- Christopher J. Elbe, Owner, Christopher & Tracy Elbe Dairy, West Bend, WI
- Carlos C. Lourenco, Owner, Carlos Lourenco Dairy, Merced, CA
- Hector Stechnij, Owner, Hector Stechnij Dairy, Mesa, AZ
- Peter J. Vander Poel, Sr., Pete Vander Poel Dairy, Tulare, CA
- Jack Hanke, Owner, Hanke Farms, Inc., Sheboygan Falls, WI
- Hein Hettinga and E. J. (Amos) Degroot, Partners, Pahrump Dairy, Pahnlmp, NV
- Mr. & Mrs. Henry A. Vander Poel, Co-Owners and John C. Vander Poel, Co-Owner, Whiteside Dairy, Wasco, CA

The above violations involved sulfadimethoxine in cows, penicillin in cows, flunixin in cows, gentamicin in cows and ivermectin in a bull.

Warning Letters were sent to the following individuals and firms for significant deviations from the Current Good Manufacturing Practice (cGMP) regulations for Medicated Feeds.

- Austin J. DeCoster, Owner, DeCoster Feeds, Turner, ME
- Donald L. Pope, President, Brookhurst Mill, Riverside, CA
- David A. Robertson, President, Allen Robertson & Company, Inc., Louisville, KY
- Rich Dwyer, President, Kent Feeds, Inc., Muscatine, IA

Warning Letters were sent to the following individuals/firms because they compounded and distributed veterinary drug products that were considered adulterated under the Federal Food, Drug, and Cosmetic Act (the Act). A new animal drug is deemed unsafe unless an approved New Animal Drug Application (NADA) is in effect for the specific product in question. None of the animal drugs compounded and distributed by these firms were the subject of an approved NADA. The only legal compounding of animal drugs is provided under the Animal Medicinal Drug Use Clarification Act and its implementing regulations at Title 21 of the *Code of Federal Regulations* (CFR) Part 530, Extralabel Drug Use in Animals.

- Dr. Warren B. Lee, President, Lee Pharmacy, Inc., Fort Smith, AR
- Mr. John R. Rains, R. Ph., CEO, Plum Creek Pharmaceuticals, Inc., Amarillo, TX
- Mr. Jack R. Munn, R. Ph., President, Medical Park Pharmacy, Dallas, TX

A Warning Letter was issued to Robert H. Douglas, Ph.D., BET Pharm LLC, Lexington, KY, because, while the firm purports to be a compounding pharmacy for veterinary drugs, FDA investigation determined that the firm exceeds the scope of the regular course of the practice of pharmacy. The firm's activities go beyond that of a pharmacy and into the activities of a drug manufacturer. The only legal compounding of animal drugs is provided under the Animal Medicinal Drug Use Clarification Act and its implementing regulations at Title 21 of the *Code of Federal Regulations* (CFR) Part 530, Extralabel Drug Use in Animals.

A Warning Letter was issued to Kenneth L. Collier, DVM, Co-owner, Friendship Valley, LLC, Clintonville, WI, because an investigation into an illegal tissue residue in a dairy cow sold for slaughter as human food by the firm revealed serious deviations from the regulations for Extralabel Drug Use in Animals. These deviations caused an animal drug to be used in a manner that was unsafe and adulterated under the Act.

A Warning Letter was issued to Timothy J. Dennis, DVM, Partner, Eastview Veterinary Clinic P.C., Penn Yan, NY, because an investigation revealed serious deviations from Extralabel Drug Use in Animals. The extralabel use of approved animal drugs by veterinarians is allowed under the Act provided that the regulations contained in 21 CFR Part 530 are followed. Extralabel use of an approved animal drug that is not in compliance with the regulations contained in 21 CFR Part 530 renders the drug unsafe under Section 512 and thus adulterated under Section 501 (a)(5) of the Act.

A Warning Letter was issued to Mr. Richard Chapman, President, North Country Dairy Supply, Inc., West Rutland, VT, for significant deviations from FDA's regulations establishing cGMPs for finished pharmaceuticals. ■

FDA Veterinarian Index Available

A topical index for the 2003 *FDA Veterinarian* is now available on the CVM Internet Home Page (*http://www.fda.gov/cvm/index/fdavet/fdavettoc.html*). Readers who wish to obtain a paper copy of the Index may call or write the *FDA Veterinarian*. ■

CVM Scientists Develop PCR Test to Determine Source of Animal Products in Feed, Pet Food

by Michael Myers, Ph.D., Research Pharmacologist, Office of Research

A test, derived to determine source of pentobarbital in pet food, is so sensitive it can identify the species of origin for animal products on a scale of 7 lbs. per 500 tons. Tests find no cat or dog DNA in pet food.

Anecdotal reports from veterinarians during the 1990s suggested pentobarbital appeared to be losing its effectiveness as an anesthetizing agent in dogs. These reports led to speculation that pentobarbital was present as a contaminant in dog food, and that this was altering the physiological response to pentobarbital-induced anesthesia in some dogs.

Pentobarbital is used to humanely euthanize unwanted animals (including dogs and cats in animal shelters) as well as animals in situations of severe pain and suffering. Pentobarbital is a member of the barbiturate family of drugs, which are proven inducers of drug metabolism. Agents that induced drug metabolism enhance the metabolism and elimination of drugs from the body, which has a net effect of decreasing the effectiveness of those drugs. While pentobarbital is a weak inducer of drug metabolism, there was speculation that the dogs had been exposed somehow to pentobarbital, which increased the dogs' metabolism to the drug to cause reduced effectiveness. Until recently, carcasses from pentobarbital-euthanized animals were disposed of by rendering. Pentobarbital is known to survive the rendering process and partition equally into protein and fat[1].

Scientists working at the Food and Drug Administration's Center for Veterinary Medicine developed an analytical method for the determination of pentobarbital residues in dog food, and in a limited survey found that several lots of commercial dog food contained confirmable levels (10-60 parts per billion) of pentobarbital[2]. These results confirmed an earlier study that also found detectable levels of pentobarbital in dry dog food samples[3]. Thus, one of the two central premises for why pentobarbital could be losing effectiveness—the presence of pentobarbital in dry dog food—was demonstrated.

However, the second premise, namely auto-induction of drug metabolism, could not be demonstrated. In a toxicological study designed to answer this very question, FDA scientists demonstrated that pentobarbital could affect the drug metabolizing system of dogs, but only at greatly elevated levels of pentobarbital[4]; i.e., at levels well above those possible by prolonged consumption of dog food containing the highest levels of pentobarbital.

PCR-based Test

These studies did not address the central question of the source of the pentobarbital in dog food. It has been presumed that pentobarbital was present in these dog food samples because euthanized animals, such as dogs, cats, and horses, might be included with other animal-byproducts used in preparing dog food. However, this presumption was difficult to test due to the limitations of existing analytical methods. Therefore, CVM scientists developed a polymerase chain reaction (PCR)-based approach to identify species-specific products that might be present in dog food.

The approach the scientists used was a modification of the PCR-based method validated for detecting bovine-derived materials in complete animal feed.[5] The polymerase chain reaction is an *in vitro,* test-tube diagnostic approach using DNA precursor molecules, two distinct oligonucleotides (termed "primers"), magnesium ions, the template or target DNA, and DNA polymerase, the enzyme that catalyzes the process.

The PCR primers are short, synthetic stretches of DNA that bind to the template DNA. The primers are designed to bind to only one particular section of DNA, such that with repeated cycles of amplification, logarithmic increases in the DNA sequence between where the primers bind are produced. This results in an easily detectable level of product.

Because of the specificity of the primers, it is possible to detect not only one genetic sequence in an organism's entire genome, but to determine from which species of several closely related species a particular DNA sequence was derived.

The underlying principle of the method we developed is the amplification of a mitochondria-specific DNA sequence (mtDNA) using PCR primer pairs that permit species-specific amplification.

Mitochondria are small organelles found in eukaryotes which are responsible for directing cellular respiration. Mitochondria are more commonly called "the cells' powerhouse" because of their unique role in generating the energy sources used by cells. Mitochondria

(Continued, next page)

. . . CVM Scientists Develop PCR Test *(Continued)*

have their own DNA called mitochondrial DNA (mtDNA) which is distinct from genomic DNA. The genes encoded by mtDNA are used to control cell respiration. Genomic DNA is equally inherited from both parents, while mtDNA comes only from the mother.

The use of mtDNA sequences increases the number of targets available for amplification relative to genomic DNA, which increases the sensitivity of the method. This approach is possible because there are roughly 50-100 mitochondria in each cell, all having a copy of mtDNA.

In addition, each mitochondria may have up to 100 copies of mtDNA, for a potential of 2,500-10,000 copies of mtDNA per cell, compared with a single copy of a given genomic DNA sequence.

Accordingly, PCR primers specific for canine, equine, or feline mtDNA sequences were developed and used to test for the possible presence of rendered materials from these species in dog food.

In addition, other species-specific PCR primers were used to assess the accuracy of the label claims by comparing the PCR results with the ingredient statements from the package label.

Looking for Canine DNA

A PCR primer set specific for a canine mtDNA sequence was deduced, and subsequently shown to amplify only that mtDNA derived from dogs, but not mtDNA derived from cattle, swine, sheep, goat, pig, cat, deer, elk, poultry, turkey, rabbit, or horse blood (Fig 1).

When the PCR process is applied to a sample, researchers look for the process to yield PCR products called amplicons that are specific both to the animal species and gene sequence the researchers are looking for.

Thirty-one dog food samples previously analyzed for the presence of pentobarbital[2] were then subjected to the DNA extraction process and tested for the presence of canine DNA. The results demonstrated the complete absence of canine DNA in all 31 samples (Fig 2) at a level exceeding 0.0007% (w/w). In other words, at this level of detection, we can say that if there is any canine material in the dog food, it is present at a rate of less than 7 lb. per 500 tons.

Cats and horses are also euthanized with pentobarbital and thus might be the source of this drug in dog food. PCR primer sets that are specific for either feline or equine mtDNA were also developed to test the same dog food samples for presence of mtDNA that might have been derived from cats or horses. The results from these analyses demonstrated the complete absence of PCR products, the amplicons, specific for either cat or horse mtDNA in all 31 dog food samples. This analysis was carried out under conditions that achieved 0.007% sensitivity.

Because the results so far were negative, it was important to demonstrate that mtDNA from these dog food samples could be amplified to increase the sensitivity of the test. Therefore, the mtDNA from these samples were subjected to PCR amplification using a set of PCR primers (termed "universal" primers) shown to amplify only mtDNA from cow, deer, elk, sheep, goat, horse and pig. These particular animal species were expected to be present in the samples due to the ingredient statements of the dog food labels.

The results demonstrated that most, but not all, samples had a PCR amplicon, indicating that one or more of these species (cow, deer, elk, sheep, goat, horse or pig) were present in these dog food samples. Interestingly, two samples that were positive for pentobarbital did not produce a PCR amplicon when the universal primers were used, suggesting a complete absence of mammalian-derived mtDNA from species that are typically euthanized with pentobarbital.

Using PCR primer sets specific for bovine, swine, or sheep mtDNA, we were able to demonstrate the presence of rendered material derived from one or more of these species. As expected, samples that did not produce a PCR amplicon using the universal primers failed to produce amplicons when the species-specific primers were used.

For the most part, the PCR results confirmed the ingredients as listed on the package label. Unexpectedly, there were four samples that had PCR results inconsistent with the package label.

Two dog food samples listed lamb in the label, yet both samples also had a PCR amplicon specific for bovine mtDNA. One of the samples labeled as containing lamb proteins produced no amplicon specific for sheep (lamb). While the remaining two samples listed only poultry on the label, one sample had a PCR amplicon specific for bovine mtDNA, whereas the other sample had a PCR amplicon specific for swine mtDNA. Pentobarbital was present in these latter two samples.

No Dog or Cat mtDNA

It is widely presumed that the principal source of pentobarbital in pet food is the rendered remains of animals euthanized at animal shelters. However, the absence of detectable feline or canine mtDNA in the samples indicates that, within the context of this limited survey, rendered proteins from euthanized dogs and

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. . . CVM Scientists Develop PCR Test *(Continued)*

cats were not present in these dog food samples. The detection limit of the method as used in this study is, at a minimum, 0.0007% on a w/w basis, or 7 lbs. of rendered protein in 500 tons of dog food. While one can argue that there may be the rendered remains of dogs or cats below this level, this amount of rendered meat and bone meal (less than 7 lbs.) is insufficient to produce the levels of pentobarbital detected in some of these dog food samples.

Horses are the other animal species euthanized with pentobarbital in relatively large numbers. Due to their large size, and the amount of drug needed for euthanasia, one horse would represent a significant portion of a large batch of meat and bone meal. However, none of the 31 dog food samples examined in this study tested positive for equine proteins.

Also, none of the samples was positive for feline proteins.

Thus, the pentobarbital found in 10 of these 31 dog food samples does not appear to be due to contamination of meat and bone meal containing the remains of euthanized dogs, horses, or cats.

In fact, the PCR results on the species of origin in the various dog food samples do not support a single point source of protein for the origin of the pentobarbital.

The only common feature of all samples containing pentobarbital is the presence of animal fat. This suggests that animal fat might be the source for pentobarbital. This hypothesis is supported by observations from the initial survey for pentobarbital in dog food. A positive relationship was noted between the ingredients listed on the package label and the likelihood a sample contained pentobarbital (*http://www.fda.gov/cvm/efoi/DFreport.htm*).

While the results of this study narrow the search for the source of pentobarbital, it does not define the source (i.e., species) responsible for the contamination.

This PCR method developed by FDA scientists can also be used in assuring the validity of label claims on feed or pet food.

Twenty-seven of the 31 samples showed agreement between the PCR results and the package label for mammalian and avian derived components. In only four samples did the PCR results not agree with the label claims. In all four cases, bovine materials were noted by the PCR results; there were no bovine protein sources listed on the labels for these samples. However, these samples all list either animal fat or beef tallow on the label, suggesting that this component might be the source of the bovine material. Residual levels of animal derived proteins contaminating the animal fat might explain these findings; whether this is the case or not cannot be determined at present.

The absence of a PCR amplicon in these samples could also be due to experimental error or sample

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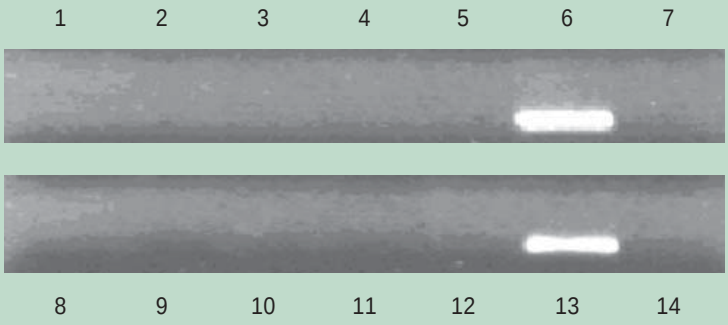
FIGURE 1.
Specificity of Canine mtDNA Primers



Detection of canine mitochondrial DNA using PCR primers specific for *Canis familiaris*. PCR primers specific for *Canis familiaris* were used to amplify mtDNA obtained from numerous species. The PCR product was separated in a 2% agarose gel containing ethidium bromide. Lanes 1-7 (top picture) contained DNA obtained from the blood of cattle, elk, horse, goat, sheep, dog (beagle), and pig, respectively. Lanes 8-14 (bottom picture) contained DNA obtained from the blood of chicken, geese, cat, rabbit, turkey, dog (mixed breed), and deer, respectively. Only mtDNA from the two dogs produced a PCR amplicon. Similar results were obtained when either the feline-specific primers or the equine-specific primers were used. That is, these latter primers only amplified mitochondrial DNA from their respective species.

. . . CVM Scientists Develop PCR Test *(Continued)*

misbranding. Based on previous results, the rate of false negatives and false positive for this method is 1.25% and 0.83%, respectively.[4] However, these samples were analyzed by two different investigators on two different occasions, with both analysts obtaining the same result, suggesting that the product is incorrectly labeled (i.e. misbranded or adulterated).

Conclusion

The results of this study demonstrated a lack of correlation between species identity and the presence of pentobarbital in dog food. They also provide evidence against the presumption that euthanized pets are routinely rendered and used in pet food.

In addition, the results of this study have established a methodology for identification of the types (re: species) of meat and bone meal present in dog food. This method should prove useful for analysis of dog (and cat) food for the accuracy of the label claims.

References

1 O'Connor JJ, Stowe CM, Robinson RR. Fate of sodium pentobarbital in rendered products. *Am J Vet Res* 1985; 46:1721-1724.

2. Heller DN, Lewis KM, Cui W. Method for determination of pentobarbital in dry dog food by gas chromatography/mass spectrometry. *J Agric Food Chem* 2001; 49:4597-602.
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4. Kawalek JK, Howard KD, Farrell DE, Derr J, Cope CV, Jackson J, Myers MJ. Effect of low doses of pentobarbital in beagles. *Am J Vet Res* 2003; .
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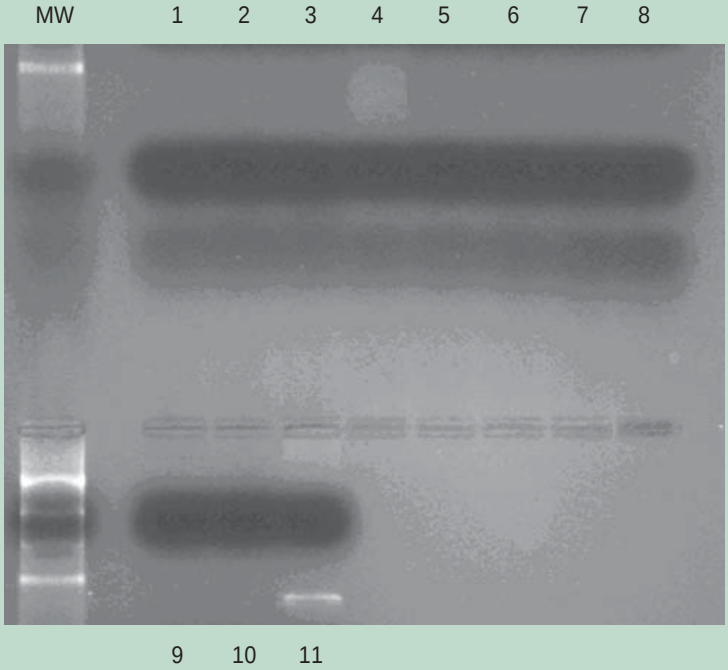
FIGURE 2.
Analysis of Dog food Samples



PCR analysis for canine mtDNA in dog food. Representative results from some of the 31 different dog food samples analyzed. The 10 samples shown here had previously been found to contain pentobarbital (2). The DNA from the dog food samples was extracted and subjected to PCR amplification using the canine specific PCR primers. The PCR product was separated in a 2% agarose gel containing ethidium bromide. MW; molecular weight standards. Lanes 1-9, dog food samples. Lane 10, negative control. Lane 11, purified canine DNA (positive control). Only the positive control sample (Lane 11) demonstrated the presence of a PCR amplicon.

Ask CVM

The CVM Home Page receives quite a bit of mail. The questions and answers featured here are composites of multiple questions the Home Page has received on the same topic. If you would like to send a question to the CVM Home Page, please visit ***www.fda.gov/cvm*** *and select "contact CVM," or write us directly at* ***CVMHomeP@cvm.fda.gov****.*

We have developed a device for use in horses for use with homeopathic medication and pharmaceuticals. The device will be sold without any medication. Does FDA have to approve the product before it can be sold in the U.S.?

No prior approval is required for devices. According to information on FDA's website *(www.fda.gov/cvm/index/consumer/regofdevices.htm*), "The FDA does not require submission of a 510(k) or formal pre-market approval for devices used in veterinary medicine. Firms that manufacture radiation emitting devices need to register their products under the radiological health regulations, administered by the Center for Devices and Radiological Health. (See *www.fda.gov/cdrh/devadvice/311.html*)

"Device manufacturers who exclusively manufacture or distribute veterinary devices are not required to register their establishments and list veterinary devices.

"FDA does have regulatory oversight over veterinary devices and can take appropriate regulatory action if a veterinary device is misbranded, mislabeled, or adulterated.

"It is the responsibility of the manufacturer and/or distributor of these articles to assure that these animal devices are safe, effective, and properly labeled.

"FDA recommends that devices should meet or be equivalent to the performance standards. This is especially important for devices that can be used both in humans and animals, such as examination gloves, sterile catheters, infusion pumps, etc."

The Federal Food, Drug, and Cosmetic Act defines medical devices as *"an instrument, apparatus, implement, machine, contrivance, implant,* in-vitro *reagent, or other similar or related article, including any component, part, or accessory thereof, which is intended for use in the diagnosis of disease or other conditions; in the cure, mitigation, treatment, or prevention of disease in man or other animals; or which is intended to affect the structure or any function of the body of man or other animals."* Examples of devices include such things as needles, syringes, surgical instruments, prosthetic devices, X-ray equipment, certain diagnostic test kits, and dental appliances.

I am developing a line of pet grooming products (shampoos and conditioners) and am trying to find out if there are any FDA labeling requirements or laws that apply to such products.

The animal counterpart of a cosmetic is commonly referred to as a "grooming aid." The Act defines cosmetics as pertaining only to human use (201(i)). Therefore, products intended for cleansing or promoting attractiveness of animals are not subject to FDA control. However, if such products are intended for any therapeutic purpose or if they are intended to affect the structure or function of the animal, they are considered drugs and would be subject to regulation as new animal drugs under the Federal Food, Drug & Cosmetic Act.

What should I do if I find a pet food product that is defective?

You should contact the complaint coordinator at the FDA District Office in your area. You can find information about this program and a listing of the complaint coordinators at *www.fda.gov/opacom/backgrounders/complain.html*. We also suggest that you contact the pet food company so it is aware of the complaint.

FDA Releases Jan. 23 Figures on Compliance With BSE Rule

As of January 23, 2004, the Food and Drug Administration had received more than 26,000 reports of inspections conducted under the BSE feed rule, first implemented in 1997, according to information the Center for Veterinary Medicine released in early February.

To enforce the rule concerning BSE, FDA inspects renderers, feed mills, and other types of firms to ensure compliance with the BSE feed rule.

The majority of these inspections reported (around 70%) were conducted by State officials under contract to FDA, with the remainder conducted by FDA officials.

Inspections conducted by FDA or State investigators are classified to reflect the inspected firm's compliance status at the time of the inspection based upon the objectionable conditions documented. These inspection conclusions are reported as Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or No Action Indicated (NAI).

An OAI inspection classification occurs when significant objectionable conditions or practices are found and regulatory sanctions are warranted in order to address the establishment's lack of compliance with the regulation. An example of an OAI inspection classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspections classified with OAI violations will be promptly re-inspected following the regulatory sanctions to determine whether adequate corrective actions have been implemented.

A VAI inspection classification occurs when objectionable conditions or practices are found that do not meet the threshold of regulatory significance, but do warrant advisory actions to inform the establishment of findings that should

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FDA Releases Figures on BSE Compliance *(Continued)*

be voluntarily corrected. Inspections classified with VAI violations are more technical violations of the 1997 BSE feed regulation provisions, such as minor recordkeeping lapses and conditions involving non-ruminant feeds.

A NAI inspection classification occurs when no objectionable conditions or practices are found during the inspection or the significance of the documented objectionable conditions found does not justify further actions.

The results to date are reported here both by "segment of industry" and "in total."

Renderers: These firms are the first to handle and process (i.e., render) animal proteins and to send these processed materials to feed mills or protein blenders for use as a feed ingredient.

- Number of active firms whose initial inspection has been reported to FDA – 235.
- Number of active firms handling materials prohibited from use in ruminant feed – 157 (67% of those active firms inspected).
- Of the 157 active firms handling prohibited materials, their most recent inspection revealed that
  - 0 firms (0%) were classified as OAI,
  - 3 firms (1.9%) were classified as VAI.

Licensed feed mills: FDA licenses these feed mills to produce medicated feed products. The license is required to manufacture and distribute feed using certain potent drug products, usually those requiring some pre-slaughter withdrawal time. This licensing has nothing to do with handling prohibited materials under the feed ban regulation. A medicated feed license from FDA is not required to handle materials prohibited under the BSE feed rule.

- Number of active firms whose initial inspection has been reported to FDA – 1,085.
- Number of active firms handling materials prohibited from use in ruminant feed – 310 (29% of those active firms inspected).
- Of the 310 active firms handling prohibited materials, their most recent inspection revealed that:
  - 0 firms (0%) were classified as OAI,
  - 7 firms (2.2%) were classified as VAI.

Feed mills not licensed by FDA: These feed mills are not licensed by the FDA to produce medicated feeds.

- Number of active firms whose initial inspection has been reported to FDA – 5,071.
- Number of active firms handling materials prohibited from use in ruminant feed – 759 (15% of those active firms inspected).
- Of the 759 active firms handling prohibited materials, their most recent inspection revealed that
  - 4 firms (0.5%) were classified as OAI,
  - 39 firms (5.1%) were classified as VAI.

Protein blenders: These firms blend rendered animal protein for the purpose of producing quality feed ingredients for use by feed mills.

- Number of active firms whose initial inspection has been reported to FDA – 252.
- Number of active firms handling materials prohibited from use in ruminant feed — 71 (28% of those active firms inspected).
- Of the 71 active firms handling prohibited materials, their most recent inspection revealed that
  - 0 firms (0%) were classified as OAI,
  - 2 firms (2.8%) were classified as VAI.

Renderers, feed mills and protein blenders: This category includes any firm that is represented by any of the above four categories, but includes only those firms that manufacture, process, or blend animal feed or feed ingredients using prohibited materials.

- Number of active renderers, feed mills and protein blenders whose initial inspection has been reported to FDA - 6,465.
- Number of active renderers, feed mills and protein blenders processing with prohibited materials – 540 (8.3% of those active firms inspected).
- Of the 540 of active renderers, feed mills and protein blenders processing with prohibited materials, their most recent inspection revealed that
  - 5 firms (0.9%) were classified as OAI,
  - 24 firms (4.4%) were classified as VAI.

Other firms inspected: Examples of such firms include ruminant feeders, on-farm mixers, pet food manufacturers, animal feed salvagers, distributors, retailers, and animal feed transporters.

- Number of active firms whose initial inspection has been reported to FDA – 9,781.
- Number of active firms handling materials prohibited from use in ruminant feed – 1,396 (14% of those active firms inspected).
- Of the 1,396 active firms handling prohibited materials, their most recent inspection revealed that
  - 5 firms (0.4%) were classified as OAI,
  - 68 firms (4.9%) were classified as VAI.

Total firms: (Note: A single firm can be reported under more than one firm category; therefore, the summation of the individual OAI/VAI firm categories will be more than the actual total number of OAI/VAI firms, as presented below.)

- Number of active firms whose initial inspection has been reported to FDA – 13,672,
- Number of active firms handling materials prohibited from use in ruminant feed – 1,949 (14% of those active firms inspected),
- Of the 1,949 active firms handling prohibited materials, their most recent inspection revealed that
  - 5 firms (0.1%) were classified as OAI,
  - 85 firms (4.4%) were classified VAI.

Comings and Goings

NEW HIRES

- David Wardrop, Jr., Director, Office of Management
- James Minter, Ph.D., Acting Director, CVM Staff College, Office of Management

DEPARTURES

Retirements

- Don Peterson, Director, Office of Management
- Elizabeth Parbuoni, Information Technology Specialist, Office of Management
- Karen Kandra, Management Analyst, Office of the Director
- Bessie Cook, Workforce Diversity Manager, Office of the Director
- Francisca Stone, Industry Compliance Specialist, Office of Surveillance and Compliance
- Jean Jackson, Physical Science Technician, Office of Research

Other Departures

- Kendrick Gibbs, Information Technology Specialist, Office of Management
- Lorraine Malden, Program Analyst, Office of Management
- Wendy Schuller, Facilities Specialist, Office of Management
- Carole Andres, Microbiologist, Office of the Director
- Treava Hopkins, Workforce Diversity Specialist, Office of the Director
- Scheryl Sledge-Gonzales, EEO Specialist, Office of the Director

Food Additive Regulations Amended – Formaldehyde

In the November 21, 2003, *Federal Register*, the FDA announced that the Agency is amending the food additive regulations to provide for the safe use of formaldehyde to improve the handling characteristics of canola and soybean oilseeds and/or meals in feed for beef and dairy cattle, and to provide a description of the food additive. This action is in response to a food additive petition filed by Rumentek Industries Pty Ltd.

New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Pharmacia & Upjohn Co. (NADA 141-209)	Ceftiofur crystalline free acid sterile suspension (NAXCEL XT) Rx	Beef and Non-lactating Dairy Cattle. For the treatment and control of bovine respiratory disease.	**INJECTABLE—**The NADA provides for the veterinary prescription use of ceftiofur crystalline free acid suspension in beef and non-lactating dairy cattle for the treatment of BRD (shipping fever, pneumonia) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Haemophilus somnus* and for the control of respiratory disease in cattle at high risk of developing BRD associated with M. *haemolytica*, *P. multocida*, and *H. somnus*. *Federal Register* 10/22/03
Intervet, Inc. (NADA 141-222)	Altrenogest oral solution (MATRIX)	Gilts (sexually mature gilts that have had at least one estrous cycle). For synchronization of estrus.	**ORAL—**The NADA provides for use of an altrenogest oral solution in gilts for synchronization of estrus. *Federal Register* 10/31/03
Boehringer Ingelheim Vetmedica, Inc. NADA 141-219	Meloxicam Injectable Solution (METACAM) Rx	Dogs. For the control of pain and inflammation associated with osteoarthritis.	**INJECTABLE—**The NADA provides for use of meloxicam injectable solution in dogs for the control of pain and inflammation associated with osteoarthritis. *Federal Register* 12/10/03

Supplemental New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Monsanto Company (NADA 140-872)	Sometribove Zinc Suspension (Posilac)	Lactating Dairy Cows. To increase the production of marketable milk.	**INJECTABLE—**The supplemental NADA provides for revised wording of the indication and precautionary labeling. The regulations are also being amended to reflect a different drug labeler code for Monsanto Co. *Federal Register* 10/31/03

Abbreviated New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Cross Vetpharm Group, Ltd. (ANADA 200-312)	Dexamethasone injectable solution (DEXIUM) Rx	Dogs, Cats, Cattle, and Horses. For the treatment of primary bovine ketosis and as an anti-inflammatory agent in dogs, cats, cattle, and horses.	**INJECTABLE—**The ANADA provides for the veterinary prescription use of dexamethasone injectable solution for the treatment of primary bovine ketosis and as an anti-inflammatory agent in dogs, cats, cattle, and horses. Cross Vetpharm Group's DEXIUM Solution is approved as a generic copy of Schering-Plough Animal Health's AZIUM Solution 2 milligrams, approved under NADA 12-559. *Federal Register* 11/19/03
Norbrook Laboratories, Ltd. (ANADA 200-308)	Flunixin Injection Rx	Horses, Beef cattle, and Non-lactating Dairy Cattle. For the control of inflammation.	**INJECTABLE—**The ANADA provides for the veterinary prescription use of flunixin meglumine injectable solution for the control of inflammation in horses, beef cattle, and non-lactating dairy cattle. Norbrook Laboratories' Flunixin Injection is approved as a generic copy of Schering-Plough Animal Health's BANAMINE (flunixin) Solution, approved under NADA 101-479. *Federal Register* 12/19/03

Supplemental Abbreviated New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Phoenix Scientific, Inc. (ANADA 200-247)	Oxytetracycline Hydrochloride Soluble Powder	Honeybees. For the control and treatment of foulbrood. Swine. In drinking water for the treatment of various bacterial diseases.	**ORAL —**The supplement provides for use of oxytetracycline hydrochloride soluble powder in honeybees for the control and treatment of foulbrood, and in swine drinking water with a reduction in pre-slaughter withdrawal time to zero days. *Federal Register* 12/10/03

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