FDA VETERINARIAN
Center for Veterinary Medicine
2007 Vol. XXII, No. VI

Dr. Bernadette Dunham Takes the Reins as CVM's New Director

by Walt D. Osborne, M.S., J.D., Assistant Editor

Referring to her as a "world class scientist and leader," Commissioner of Food and Drugs Dr. Andrew von Eschenbach appointed Dr. Bernadette Dunham to head FDA's Center for Veterinary Medicine, effective January 7, 2008. She steps up from Deputy Director of CVM, replacing Dr. Stephen Sundlof, who was appointed to head the Agency's Center for Food Safety and Applied Nutrition, effective the same day.

With extensive experience in the food safety and protection area, Dr. Sundlof is well suited to serve as CFSAN's Director. He provided significant input into the development of FDA's Food Protection Plan that was unveiled last year, and has also been instrumental in putting strong animal feed programs into place to prevent Bovine Spongiform Encephalopathy (BSE) from entering the United States. He led CVM for 14 years, and will be sorely missed by all who knew and worked with him there. One of his legacies at CVM will be the implementation of the principals of "High Performance Organization" (HPO), which all CVM employees are encouraged to live by and which has engendered the fairly widely heard mantra of "CVM is the best Center to work for."

But who is Dr. Dunham, what makes her tick, and what keeps that energetic bounce in her step all day long? I had a chance to sit down with this remarkable dynamo recently to get some answers to those and many other questions.

Bernadette Dunham, D.V.M., Ph.D., became Director, Center for Veterinary Medicine, in January.

First of all, she is no stranger to CVM, having worked closely with Dr. Sundlof in her role as Deputy Director since 2006. She has played a critical role in coordinating and establishing Center policy in research, management, scientific evaluation, compliance, and surveillance.

She has also been serving as the director for CVM's Office of Minor Use and Minor Species (MUMS) Animal Drug Development. This is the office that oversees drug development for such species as zoo animals, ornamental fish, parrots, ferrets, guinea pigs, sheep, goats, catfish, and honeybees. The MUMS office also oversees drug development for uncommon diseases in the major species: cattle, pigs, chickens, turkeys, horses, dogs, and cats.

Dr. Dunham has turned over the position of Director of the Office of MUMS to Dr. Meg Oeller, who will serve as acting director. Dr. Oeller has been part of the MUMS office since it was initiated.

No stranger to veterinary medicine

Dr. Dunham, who holds a Doctor of Veterinary Medicine and a Ph.D. in cardiovascular physiology, joined CVM in 2002, serving as the Deputy Director of the Office of New Animal Drug Evaluation. Prior to this, she served in several important leadership positions with the American Veterinary Medical Association and held faculty positions at several universities, including in the Department of Pharmacology at the State University of New York Health Science Center at Syracuse. Early on,

(Continued, next page)

In This Issue

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

...CVM's New Director *(Continued)*

Dr. Dunham worked as a veterinarian in private practice, so she has seen just about every facet of the profession – hands-on veterinary work, research, teaching, congressional liaison work, and federal service. She brings to the Director position, not only exemplary credentials, but also a true passion for human and animal health and for carrying out FDA's mission.

"I pinch myself every day since Dr. Sundlof passed the CVM reins to me," Dr. Dunham enthusiastically commented. She said she is excited about continuing the many projects and initiatives that Dr. Sundlof has put into place as CVM Director over the past 14 years. The new CVM Director freely expressed her sincere enthusiasm about working with what she terms "incredibly dedicated and talented people" at the Center. She also said that she is anxious to put "our face" in public view so that CVM's many stakeholders can see for themselves who we really are.

Meeting certain challenges head-on are priorities for 2008. Most notable of these is addressing food and feed safety in light of the melamine incident of 2007 and the directives from Congress that are embodied in the recently enacted legislation ("The Food and Drug Administration Amendments Act of 2007" [FDAAA]) designed to ensure that melamine-type scenarios do not present themselves again.

Pet food recall was a learning tool

"CVM does not work in a vacuum, and we will be interacting with our partners on this new food safety initiative, including feed groups, pet owners, pharmaceutical companies, and the public – something I truly look forward to doing," Dr. Dunham stated. She spoke of the many lessons learned from last year's massive pet food recall that was sparked by the melamine-contaminated wheat gluten in so many products. The recall is one of the more significant driving forces behind FDA's Food Protection Plan, the key tenets of which are prevention, intervention, and response. Dr. Dunham noted that during the pet food recall, FDA found itself responding first, and then looking at intervention and prevention measures. With FDA's Food Protection Plan, prevention will be the first step, thus reducing the need for intervention and response.

Another lesson learned from the pet food recall, according to Dr. Dunham, was how integrated the Agency's animal feed and human food systems really are. "We saw how the feed distribution chains are complex and often overlap and how the contaminant, melamine, ended up in pet food and the feed supply for food production animals. Fortunately, we averted what could have been a problem for human food," Dr. Dunham added. For this reason, she foresees close collaborative efforts with CFSAN to coordinate food and feed protection across the Agency, which are pivotal to ensuring that future problems either do not arise or, if they do, are quickly resolved.

Risk communication

One of the key challenges Dr. Dunham sees for CVM is communicating the risk associated with products in a manner that is scientifically accurate yet easily understandable by people without a scientific background. This need was illustrated so vividly by the pet food recall, which involved a massive public information effort and the interplay of so many different FDA players. "Staff from CVM, the Agency's Office of Regulatory Affairs, and the Office of Public Affairs among others worked 24-7 to answer phones, respond to e-mails, constantly update the Web site, and liaison with the affected companies in an effort to keep our messages consistent and to reassure the public," Dr. Dunham said. "And the whole effort was very stressful, too, because peoples' pets were involved; and as veterinarians, we are keenly sensitive to the importance of companion animals," she added. She also mentioned the need to always continue fine-tuning our messages to the public, because no matter how strong the effort, there is always room for improvement in this area.

Pet owners want the best treatment

Dr. Dunham noted that pet owners are increasingly demanding the best possible medical treatment for their pets, so the challenges CVM faces with respect to innovative product approvals and treatment modalities will spill over into the veterinarian profession as well. As more and more break-through medical products enter the marketplace, especially in such fields as biotechnology, pharmacogenomics, and oncology, veterinarians will also be directly involved in the challenges of risk awareness and risk communication, Dr. Dunham explained. "We welcome partnering with the veterinary profession in this arena and assisting in any way we can," she added.

The first woman to head CVM

FDA has had many women as Center Directors, but it is no secret that Dr. Dunham is the first woman to head

(Continued, next page)

FDA VETERINARIAN

Andrew C. von Eschenbach, M.D.
Commissioner of Food and Drugs

Bernadette Dunham, D.V.M., Ph.D.
Director
Center for Veterinary Medicine

Jon F. Scheid, Editor
Walt Osborne, M.S., J.D., Assistant Editor
Richard L. Arkin, J.D., Assistant Editor

Published bi-monthly.
Articles are free of copyright and may be reprinted.
Comments are invited.
Home Page http://www.fda.gov/cvm/
Phone (240) 276-9300
FAX (240) 276-9115 or write to:
FDA Veterinarian (HFV-3)
7519 Standish Place
Rockville, MD 20855

FDA's Animal Cloning Documents Underscore Safety of Meat and Milk From Cloned Animals

by Walt D. Osborne, M.S., J.D., Assistant Editor

Meat and milk from clones of adult cattle, pigs, goats, and their offspring are as safe to eat as food from conventionally bred animals, according to three documents the Food and Drug Administration released on January 15, 2008. The release of these documents—a risk assessment, a risk management plan, and a guidance for industry—constitutes FDA's position with respect to the effect of cloning on animal and food safety, and describes the Agency's enforcement posture.

How clones are made

An animal clone is a genetic copy of a donor animal, similar to identical twins but born at a different time. Most cloning today uses a process called somatic cell nuclear transfer (SCNT). Just as with *in vitro* fertilization, scientists take an immature egg from a female animal (often from ovaries obtained at the slaughterhouse). But instead of combining it with sperm, they remove the nucleus (which contains the egg's genes). This leaves behind the other components necessary for an embryo to develop. Scientists then add the nucleus containing the desirable traits from a cell obtained from the animal the farmer wishes to copy. After a few other steps, the donor nucleus and egg fuse, start dividing, and an embryo begins to form. The embryo is then implanted in the uterus of a surrogate dam (again the same as with *in vitro* fertilization), which carries it to term. ("Dam" is a term that livestock breeders use to refer to the female parent of an animal). The clone is delivered just like any other baby animal.

Cloning is not the same as genetic engineering, which involves altering, adding or deleting DNA; cloning does not change the gene sequence. Clones are intended to be used as elite breeding animals to introduce desirable traits into herds more rapidly than would be possible using conventional breeding. Because cloned animals are intended to be used for breeding, they are not expected to enter the food supply in any significant numbers. Instead, their sexually reproduced offspring will be used for producing meat and milk for the marketplace. FDA is currently recommending that food from clones of species other than the three mentioned in the risk assessment be kept out of the food and feed chain because sufficient information to make a decision on the food consumption risks is not available.

Risk assessment

The risk assessment that was released in mid-January finds that meat and milk from clones of cattle, pigs, and goats, and food from the sexually reproduced offspring of clones pose no increased food consumption risks relative to comparable products from conventionally bred animals. The risk assessment was peer-reviewed by a group of independent scientific experts in cloning and animal health, and they agreed with the methods used by FDA to evaluate the data and the conclusions presented in the document.

Also included in the risk assessment is an overview of assisted reproductive technologies widely used in animal agriculture, the scientific information available on the health of animal clones and their sexually reproduced offspring, and an assessment of whether food from clones or their sexually reproduced offspring could pose food consumption risks that are different from the potential risks presented by food from conventionally bred animals. The conclusions drawn all agree with those contained in a 2002 report released by the National Academy of Sciences.

Risk management plan

The risk management plan addresses such topics as the risks to animal health and potential remaining uncertainties associated with food and feed from animal clones and their offspring. These risks have been observed in other assisted reproductive technologies already in use in common agricultural practices in the United States. FDA is collaborating with professional and scientific societies with expertise in animal health and reproduction to develop a set of care standards for animals involved in the cloning process.

Guidance for industry

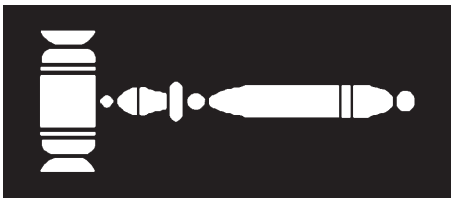
The guidance for industry, which went into effect upon publication in

(Continued, next page)

...CVM's New Director *(Cont.)*

CVM, and she views this as just another plus about the job. "I was only one of 15 women in my veterinary school class of 1982, and with this new opportunity unfolding before me, I hope to make the veterinary profession proud and to do it justice on behalf of all women," she commented. Even though it may be a little premature to be talking about a legacy, Dr. Dunham said that she hopes to be able to look back one day and feel proud and assured that she was able to be part of the sustenance and nurturing of CVM and advancing its important mission. "If I could do that, I would be floating," she added. I have no doubts that Dr. Dunham will get her wish. ■

Regulatory Activities



Warning Letters

FDA has issued a WARNING LETTER to John Visser, owner of the Visser Ranch, Strathmore, CA, for violations of the adulteration provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA). Specifically, Mr. Visser sold a bob veal calf for slaughter as human food that, upon inspection by the U.S. Department of Agriculture (USDA), was found to contain residues of the drug neomycin in the kidney tissue at 14.95 parts per million (ppm) and sulfamethoxazole in the liver tissue at 0.91 ppm and in the muscle tissue at 0.58 ppm. A tolerance of 7.2 ppm has been established for residues of neomycin in the kidney tissue (21 CFR 556.430); no tolerance has been established for residues of sulfamethoxazole in the edible tissues of cattle. The presence of these drugs at the levels indicated rendered the animal adulterated under Section 402(a) of the FFDCA. In addition, other drugs at the Visser ranch were not used in conformance with their approved labeling with respect to extralabel use parameters set forth in Section 512(a) of the FFDCA and 21 CFR Part 530.

A WARNING LETTER has been issued to William J. Behnken, CEO of American Nutrition, Inc., of Ogden, UT, for violations of the misbranding provisions of the FFDCA. Specifically, an FDA inspection revealed that some of the baked, dry extruded, and canned pet food products manufactured by the firm under its own label are in violation of Section 403(i) of the FFDCA because they are made from two or more ingredients and their labels fail to declare the common or usual name of each ingredient. At issue was the addition of rice protein concentrate to certain dog food products. This ingredient, however, is mentioned in the label, yet the label did not state "Grain

(Continued, next page)

...Safety of Meat and Milk From Cloned Animals *(Cont.)*

the *Federal Register*, addresses the use of food and feed products derived from clones and their offspring. It is directed at clone producers, livestock breeders, ranchers, and farmers who purchase clones. It provides FDA's current thinking on the use of clones and their offspring in human food or animal feed, and concludes that food products from the offspring of clones from any species traditionally used for food are suitable to enter the food and feed supply.

The Agency does not recommend any special measures in the guidance that relate to the use of products from cattle, swine, or goat clones as human food or animal feed. However, the guidance does recommend that edible products from sheep and any other clones not be introduced into the human food supply, because sufficient information was not available in order to make a decision on the food consumption risks.

The guidance also notes that, because of their cost and rarity, clones will be used as any other specialized breeding stock are—to pass on naturally occurring, desirable traits such as disease resistance and higher quality meat to production herds. Almost all of the food that comes from the cloning process is expected to be from sexually reproduced descendants of clones, not the clones themselves. The U.S. Department of Agriculture supports the FDA's conclusions regarding the safety of food from cattle, swine, and goat clones, but is encouraging the cloning industry to continue the voluntary moratorium on putting these foods into the food supply. The purpose of this moratorium is to allow for a sufficient period of time to bring stakeholders together in order to discuss efforts to provide a smooth and orderly market transition, as industry determines next steps with respect to marketing foods from clones.

The guidance also sets forth FDA's enforcement position with respect to cloning as follows: "Assuming that any part of SCNT or animal clones, based on being derived from SCNT, meet the statutory definition of new animal drug under the Federal Food, Drug, and Cosmetic Act, at this time, FDA does not intend to regulate any such new animal drugs. This intent not to regulate (i.e., the intent to exercise enforcement discretion) applies to both non-food and food-producing species."

Labeling

FDA is not recommending any additional measures relating to food derived from adult clones and their offspring, including labeling. Under the Agency's current laws, the only grounds for labeling food are if there are any safety concerns or if there is a material difference in the composition of food. FDA has not identified any food safety concerns and has not found any material difference in food from clones as food from conventionally bred animals. For instance, FDA scientists found that the milk components from dairy clones were of the same type and present in the same amounts as milk sold every day. Therefore, there is no science-based reason to use labels to distinguish between milk derived from clones and that from conventional animals.

Availability of the documents

The full text of FDA's cloning risk assessment, the risk management plan, and the guidance for industry, along with other pertinent information on cloning, are all available on FDA's Web site at: *http://www.fda.gov/cvm/cloning.htm*.

CVM's NSAID Brochure Available Through GSA Center

Veterinarians and consumers can get printed copies of the Center for Veterinary Medicine's brochure about the safe use of non-steroidal anti-inflammatory drugs (NSAIDs) in dogs through the GSA Federal Citizen Information Center in Pueblo, CO, CVM announced in January.

The brochure, "Treating Pain in Your Dog: Keeping Your Best Friend Active, Safe, and Pain Free," is available as single copies or in quantities of 100. They can be ordered free of charge on line at *http://www.pueblo.gsa.gov/rc/vetnsaids.html*.

"The NSAID brochure is a great resource for veterinarians who prescribe NSAIDs to their dog patients," according to Dr. Ann Stohlman, a veterinarian in CVM's Office of New Animal Drug Evaluation. "It explains the benefits as well as the side effects of NSAIDs. It will enhance communication between the dog owner and veterinarian and make for safer use of NSAIDs."

NSAIDs are effective pain relief drugs used in dogs. They are used to control the pain of osteoarthritis, and some veterinary NSAIDs are approved for the control of post-operative pain in dogs. However, as with all commonly prescribed veterinary drugs, the use of NSAIDs does carry some risk to the health of the dog. Owners should be aware of the potential problems NSAIDs can cause. The brochure describes the benefits of NSAIDS, potential problems, and the steps dog owners can take to protect the health of their pets.

The GSA Information Center disseminates information to the public in print, over the phone, via e-mail, or on the Web.

Regulatory Activities *(Continued)*

and Gluten Free" and "No Rice." Other pet food products made by the firm had similar labeling violations.

Violations of the adulteration provisions of the FFDCA were cited in a WARNING LETTER issued to Que Fullmer, owner of Fullmer Cattle Company New Mexico LLC of Muleshoe, TX. This cattle raising operation, which is actually located in New Mexico, offered animals for sale as food that were adulterated pursuant to Section 402(a) of the FFDCA. Two veal calves were found with the drug neomycin in the kidney tissue at 337.12 ppm, 1.28 ppm in the muscle tissue, sulfadimethoxine in the liver tissue at 0.49 ppm, and sulfadimethoxine in the muscle tissue at 0.60 ppm. A tolerance of 7.2 ppm has been established for residues of neomycin in the uncooked edible kidney tissue of cattle and 1.2 ppm in the uncooked edible muscle tissues of cattle as codified in 21 CFR 560.430. A tolerance of 0.1 ppm has been established for residues of sulfadimethoxine in the uncooked edible tissues of cattle as codified in 21 CFR 560.620. The firm was also cited for failing to maintain

(Continued, page 13)

Comings and Goings

New Hires

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Marshall Gagne, Staff Fellow
- Stuart Jeffrey, Staff Fellow

OFFICE OF RESEARCH

- Eric Evans, Biologist

OFFICE OF MANAGEMENT

- Tina Ennis, Education Program Specialist
- Trudie Willis, Program Analyst

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Robin Nguyen, Consumer Safety Officer
- Trudie Willis, Legal Instruments Examiner
- Douglass Oeller, Supervisory Veterinary Medical Officer

PulseNet, FoodNet, NARMS; Tools to Fight Disease, Protect Public Health

by Richard L. Arkin, J.D., Assistant Editor

Foodborne illness outbreaks are shifting from the typical point source, or "church supper," outbreak to more diffuse outbreaks. These can occur over many communities, with only a few illnesses in each, and therefore are difficult for public health authorities to track.

The nature of outbreaks has changed because food production and distribution have changed. Until recently, the food supply system consisted of local growers and local or regional processors. More recently, large food-producing facilities, often with nationwide distribution, have replaced smaller, regional facilities. Public health experts have difficulty detecting and dealing with this relatively new style of dispersed outbreak.

The Food and Drug Administration's Center for Veterinary Medicine, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA) are working in partnership to detect and combat the problems of this new type of outbreak.

These three government agencies have established federal food safety programs to improve their ability to identify and investigate outbreaks and take appropriate action. These programs, "PulseNet," "FoodNet," and "NARMS," use new laboratory, research, statistical, and analytical tools to help protect public health.

PulseNet

PulseNet is the National Molecular Subtyping Network for Foodborne Disease Surveillance. The PulseNet database consists of genomic DNA banding patterns ("fingerprints") of bacteria generated using a technique called pulsed-field gel electrophoresis (PFGE). PulseNet laboratories determine the subtype of the bacteria collected locally, search their local databases for clusters of matching isolates, and forward the data to CDC. CDC does an epidemiologic evaluation of bacteria from across the country. Public health authorities can use that evaluation to determine if clustered cases of foodborne illness are caused by the same strain of bacterium, which is important in determining the source of the outbreak.

Data derived from PulseNet's subtyping service network play an important role in the surveillance and investigation of foodborne illness outbreaks. Easier identification allows for epidemiologic investigations, product recalls, public health notifications, regulatory actions, industry improvements, and, ultimately, possible prevention of future disease. At the same time, PulseNet is a tool for developing and disseminating improved technologies for molecular fingerprinting.

PulseNet currently tracks Shiga toxin-producing *Escherichia coli*, *Listeria*, *Salmonella*, *Shigella* and *Campylobacter*. Scientists are developing protocols for two other organisms, *Vibrio* species and *Clostridium botulinum*.

One example of PulseNet in action involved 30 dog owners in Canada who developed salmonellosis. Many of the dog owners had recently given treats made from dried pig ears to their dogs. After the PulseNet data showed a connection between the illness and bacteria found on the pet treats, FDA issued a nationwide public health warning in the United States about dog-treat-related salmonellosis. Dr. Shaohua Zhao, a scientist with the Division of Animal and Food Microbiology (DAFM) in CVM's Office of Research, isolated and serotyped *Salmonella* bacteria from various brands of dog treats and established PFGE profiles of the *Salmonella* serotypes. She also later determined the antibiotic susceptibility of the serotypes found in the dog treats.

Another example of PulseNet at work involved DAFM researchers who have used the National Antimicrobial Resistance Monitoring System (NARMS) network to share PulseNet data about *Salmonella* bacteria isolated from humans and animals. These data have helped broaden understanding of the development of resistance to antibiotics. These DNA fingerprinting techniques are now used to examine the presence of drug-resistant bacteria in retail chicken, turkey, beef, and pork.

CDC created PulseNet in 1995, in cooperation with the Association of Public Health Laboratories and state public health laboratories. By early 2000, PulseNet had grown to include 46 state public health laboratories, the public health laboratories in New York, N.Y., and Los Angeles, CA, and USDA's Food Safety and Inspection Service Laboratory, as well as FDA's laboratories in the Center for Food Safety and Applied Nutrition and CVM. In addition, six provincial laboratories in Canada joined PulseNet in 1999 and 2000.

FoodNet

During the same period it created PulseNet, CDC, along with five state health departments, implemented

(Continued, next page)

PulseNet, FoodNet, NARMS... *(Continued)*

an active foodborne disease surveillance network called the Foodborne Diseases Active Surveillance Network (FoodNet) as part of a response to emerging infectious disease threats.

FoodNet is designed to help public health officials better understand the epidemiology of foodborne diseases in the United States.

The objectives of FoodNet are to:

- Determine the burden of foodborne disease.
- Monitor trends in the burden of specific foodborne illness over time.
- Attribute the burden of foodborne disease to specific foods and settings.
- Interrupt transmission during an ongoing outbreak.
- Develop and assess interventions to reduce the burden of foodborne disease.

FDA and USDA continue to be active collaborative partners with CDC and state and local laboratories in FoodNet. Currently, California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee have FoodNet sites.

NARMS

NARMS was established in 1996 as a collaborative effort among CVM, USDA, and CDC to address the continuing problem of food derived from animals commonly carrying organisms that are pathogenic to humans, but not animals. These bacteria can be resistant to antimicrobial drugs under the right conditions.

For example, *Salmonella*, *Campylobacter*, and *Escherichia coli* O157 may be found in the intestines of healthy food animals. All three bacteria can cause foodborne illness in humans. These bacteria can develop resistance when exposed to antibiotics given to the animal. These resistant bacteria can contaminate meat at slaughter and then infect humans who eat undercooked or mishandled raw meat products.

CVM, CDC, and USDA use NARMS to monitor changes in antimicrobial drug susceptibility of select zoonotic bacterial pathogens (which are animal bacteria that can transmit disease to humans) in food-producing animals, retail meats, and humans. Under the NARMS program, these bacteria are tested for susceptibility to a specific set (panel) of antimicrobial drugs important in human and animal medicine.

The NARMS program is intended to help manage antimicrobial resistance by providing data to:

- Identify changes in antimicrobial resistance patterns in zoonotic foodborne bacterial pathogens and select commensal organisms.
- Respond to unusual or high levels of bacterial resistance to antimicrobials in humans, animals, and retail meats in order to contain or mitigate resistance dissemination.
- Assist FDA in making decisions about approving safe and effective drugs for humans and animals, as well as promote prudent and judicious use of antimicrobial drugs.
- Design follow-up epidemiology and research studies to better understand the emergence and transfer of antimicrobial resistance.

NARMS also provides a national source of enteric bacteria isolates for research in diagnostic test development, discovery of new genes and molecular mechanisms associated with resistance, and the study of mobile gene elements, virulence, and colonization.

How NARMS Operates

Each year, samples are taken from a variety of sources and tested for changes in the resistance of certain enteric bacteria to selected antimicrobial drugs. Public health laboratories in all 50 states collect isolates from people suffering enteric disease. USDA collects isolates from healthy farm animals, animal clinical specimens, and carcasses of food animals at slaughter. FDA collects isolates from meat products at processing plants. Retail meat samples are collected from grocery stores and other retail outlets that sell meat.

The human isolates are sent to CDC in Atlanta, GA, for microbiological and epidemiological analyses. Food animal isolates are collected from sites across the United States and sent to USDA's Antimicrobial Resistance Research Unit in Athens, GA, for susceptibility testing. Additionally, bacterial isolates from retail meats are collected from grocery stores in 10 participating FoodNet states and sent from the FoodNet laboratories to CVM for antimicrobial drug susceptibility testing. CVM conducts the susceptibility testing of these samples at its Office of Research laboratory at the Agency's Muirkirk Research Center in Laurel, MD.

NARMS is designed so that the same kits to test isolates are used in the human, animal, and retail meat testing programs. For all isolates, testing bacteria for susceptibility to antimicrobials involves determining the minimum inhibitory concentration (MIC) for a panel of common antimicrobial agents. The MIC is the lowest concentration of a drug that will slow or stop the growth of the bacteria being tested. The higher the MIC number, the greater resistance the bacteria have.

(Continued, next page)

PulseNet, FoodNet, NARMS... *(Continued)*

Each year, FDA, CDC, and USDA evaluate the antimicrobial drugs included in the testing panels for relevance to the NARMS objectives, sometimes removing a drug from the panel and replacing it with another. CDC, USDA, and FDA are all currently testing *Salmonella*, *Escherichia coli*, *Campylobacter*, and *Enterococcus* for susceptibility to the same panel of antimicrobial drugs. The results of these tests are compared with results from previous years to look for emerging trends in resistance. NARMS reports are published annually by all three NARMS partners.

Role of DAFM

As part of the NARMS work, DAFM researchers obtain approximately 350 *Salmonella* isolates each year

(Continued, next page)

New Analytic Techniques in the Fight Against Foodborne Disease

by Richard L. Arkin, J.D., Assistant Editor

In 1993, a large outbreak of foodborne illness in the western United States affected some 800 people. Use of a new scientific technique may have kept this outbreak from growing larger and becoming more widespread.

During the 1993 outbreak, scientists at the Department of Health and Human Services' Centers for Disease Control and Prevention (CDC) used the relatively new pulsed field gel electrophoresis (PFGE) technique. PFGE identified clinical and food isolates of the *Escherichia coli* strain found in patients sickened by the foodborne illness. The technique also linked those isolates to a strain of *Escherichia coli* isolated at the same time from hamburger patties served in a large, regional, fast-food chain. Prompt identification of the cause of this outbreak may have prevented many more cases of illness.

The basic gel electrophoresis technique developed in the 1930s can be used to separate nucleic acid and protein molecules using an electric current applied to a porous gel matrix. In most cases, the gel is a cross-linked polymer whose composition and porosity are chosen based on the specific weight and composition of the target to be analyzed. When proteins or small nucleic acids are involved, the gel is usually made up of varying concentrations of acrylamide cross-linked to produce different sized mesh networks of polyacrylamide.

Electrophoresis refers to the electromotive force that is used to move the molecules through the gel matrix. By placing the molecules in depressions in the gel and applying an electric current, the molecules move through the matrix at different rates, usually based on size. Standard gel electrophoresis techniques for separating DNA molecules provided huge advantages for molecular biology research. However, many limitations existed with the standard protocol because it was unable to separate very large molecules of DNA effectively.

In 1984, researchers developed a variation on the standard protocol by introducing an alternating voltage gradient to improve the resolution of larger molecules. This technique came to be known as PFGE.

PFGE is like a standard gel electrophoresis, except that the voltage is reversed periodically (pulsed) to make each band of DNA run in the opposite direction for a set time, rather than constantly running the voltage in one direction. The development of PFGE significantly expanded the range of resolution for DNA fragments.

Following the 1993 foodborne illness outbreak, CDC developed standardized PFGE methods that could be used for "fingerprinting" bacteria isolated from sick persons and from possible sources of contamination to determine if the bacteria are similar. In 1995, with the assistance of the Association of Public Health Laboratories, CDC selected the state public health laboratories in Massachusetts, Minnesota, Washington, and Texas as area labs for a national molecular subtyping network for foodborne bacterial disease surveillance. CDC transferred its newly standardized PFGE typing and pattern analysis technology to the area laboratories so the labs could assume responsibility for subtyping foodborne pathogenic bacteria from their states and provide subtyping service to neighboring states that requested assistance.

The PFGE process now provides one of the key tools for the operations of PulseNet, FoodNet, and NARMS.

Role of NARMS in Assessing Risk of Antimicrobial Agents in Food Animals

by Dr. Jeffrey M. Gilbert, Supervisory Microbiologist and Team Leader on Microbial Food Safety Team, Office of New Animal Drug Evaluation; Dr. David G. White, Director, Division of Animal and Food Microbiology, Office of Research; and Dr. Patrick F. McDermott, Team Leader, CVM's NARMS program, Office of Research

An undesired consequence of antimicrobial use in animals is the development of antimicrobial-resistant foodborne bacteria that are human pathogens and the subsequent transmission of those bacteria to humans via food. To help address this concern, the Food and Drug Administration's Center for Veterinary Medicine in 1996 launched the National Antimicrobial Resistance Monitoring System (NARMS) for enteric bacteria (bacteria found in the digestive tract). NARMS is part of a strategy to assess the effect of antimicrobial use in animal agriculture on the evolution of antimicrobial resistance in human clinical bacterial isolates.

NARMS was designed to generate data on antimicrobial resistance trends in enteric bacteria from food animals, foods of animal origin, and humans. The data are used to inform physicians, veterinarians, and public health authorities on antibacterial drug resistance levels, including new or atypical patterns of resistance. The information can be used to design epidemiology and bacteriology research studies to understand the emergence and dissemination of resistance. In addition, the information is important for the development of public health recommendations on the use of antimicrobial drugs in food animals and humans. NARMS provides a national repository of isolates for use in research such as diagnostic test development, discovery of new genes and molecular mechanisms associated with resistance, the study of mobile gene elements, and the study of bacterial virulence and colonization.

NARMS researchers test isolates of the foodborne bacteria *Escherichia Coli*, *Salmonella*, *Enterococcus*, and *Campylobacter* from animals, humans, and retail meats to look for changes in the bacteria's resistance to antimicrobial drugs that are important in human and veterinary medicine.

NARMS is a national monitoring program that combines the activities of CVM, the Centers for Disease Control and Prevention (CDC), and the U.S. Department of Agriculture (USDA). These three components collect data on bacterial isolates from retail meats, human clinical cases, and food animals, respectively.

Retail meat samples are collected from grocery stores in states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Tennessee, and Oregon) that are participating in CDC's Foodborne Diseases Active Surveillance Network. The laboratories in those participating states forward the isolates recovered from the retail meat samples to CVM's Office of Research in Laurel, MD, for further analysis. Participating state and local health departments from all 50 states send isolates from

(Continued, next page)

PulseNet, FoodNet, NARMS... *(Continued)*

from retail meats. Researchers at DAFM subtype all of the isolates by PFGE and submit the DNA fingerprinting patterns to PulseNet. The patterns are compared to human clinical isolates through PulseNet. These studies reveal if there is a spread of resistant isolates between animals and humans or widespread dissemination of unrelated strains.

Researchers are also characterizing the genes that confer resistance. This research helps scientists understand the genetic diversity of *Salmonella* and the extent to which *Salmonella* strains move from animals to humans. It also helps scientists understand the effects antibiotic usage in animal husbandry can have on antimicrobial resistance in foodborne pathogens, as well as the mechanism of resistance-gene transfer between animal and human bacterial pathogens.

Scientists and other interested people can access NARMS data through links on the CVM home page at *http://www.fda.gov/cvm/narms_pg.html*. Human data are located on the CDC Web site at *http://www.cdc.gov/narms/*. Animal data are on the USDA Web site at *http://www.ars.usda.gov/Main/docs.htm?docid=14491*.

In addition, the agencies participating in the NARMS program hold periodic public meetings to present results and provide a forum for presentation of other related antimicrobial resistance research.

PulseNet, FoodNet, and NARMS are tools that continue to broaden our understanding of foodborne disease in a changing economy. These systems have played a key role in the multi-agency partnership to detect and combat foodborne illness.

Role of NARMS in Assessing Risk... *(Continued)*

human clinical cases to the CDC National Center for Infectious Diseases in Atlanta, GA, for testing.

USDA employees gather bacteria samples from healthy farm animals, from carcasses of food animals at slaughter, and from clinical specimens collected from animals undergoing medical treatment for infections. In addition, USDA collects samples from ground meat products at federally inspected slaughter and processing facilities. Researchers at the Agricultural Research Service/Antimicrobial Resistance Research Unit of USDA in Athens, GA, test the isolates from animals and from slaughter facilities for resistance.

Molecular epidemiology of resistance genes

Information about antimicrobial resistance phenotypes derived from the NARMS program does not indicate which of several genetic elements may underlie resistance. Therefore, researchers must characterize transmissible resistance genes at the nucleotide sequence level to determine the nature and extent to which specific gene transfer occurs among different bacteria, the consequence of selection pressure in the drug use environment, and the spread of resistance through the food-production continuum.

Genetic studies provide data needed to develop risk-assessment models and to aid in the regulatory decision-making process with regard to antimicrobial use in food animals. Transmission to humans via food is implied when the same genes are found in animal, food, and human isolates. Researchers from all three NARMS components (CVM, CDC, and USDA) perform genetic studies focusing on resistance mechanisms relevant to approved animal drugs, those conferring resistance to important classes used in human medicine, and unusual resistance phenotypes among isolates to characterize the resistance genes at the nucleotide level.

Researchers use a process called pulsed-field gel electrophoresis (PFGE) to characterize *Salmonella* and *Campylobacter* isolates received from the NARMS program. The PFGE process allows researchers to identify bacteria subtypes by creating a genetic "fingerprint" of the individual strain. Researchers use this information along with antimicrobial resistance data to determine how different strains are related, whether they came from the same sources, and how they were disseminated.

The information on the genetic fingerprint is also used to populate the "PulseNet" database. CDC created the PulseNet program in 1995 in cooperation with the Association of Public Health Laboratories and state public health laboratories. Public health authorities can use the information in PulseNet in their epidemiological investigations of foodborne disease outbreaks to determine if different cases of foodborne illness are related.

Also, researchers have exploited NARMS isolates to investigate novel molecular typing tools to help determine the animal origin of foodborne bacterial pathogens. To date, more than 2,000 isolates of *Salmonella* and *Campylobacter* have been characterized using a combination of two or more biochemical and genetic typing methods. Results from these tests indicate that certain bacteria serotypes are associated with only certain food animal groups. Antibiotics susceptibility profiles have shown certain resistance phenotypes to be occurring with particular animal hosts. And PFGE profiles coupled with antibiotic susceptibility profiles and additional genetic tests have shown specific strain types associated with a particular animal host. These data can help attribute different resistance profiles within a specific animal host, making it possible to identify sources of resistance.

Public health authorities have addressed several important epidemiological issues using NARMS data and the NARMS isolate collections, including the issues of "burden-of-illness estimates," case-control studies, emergence of new phenotypes, and antimicrobial resistance trends. Data from NARMS has helped to explain trends in antimicrobial susceptibility among *Salmonella*, *Campylobacter*, and *Shigella*; estimate the public health burden due to antimicrobial resistance in *Salmonella* and *Campylobacter*; and identify risk factors for *Campylobacter* infection. The data have also helped researchers understand the epidemiology of resistance in rare *Salmonella* serotypes and the emergence of resistance to the antimicrobial ceftriaxone.

To bolster NARMS data used to support FDA risk assessment models and to better understand causes of resistance, researchers have conducted studies to evaluate the effects of antimicrobial use on the evolution of resistance in foodborne bacteria residing within the target food animal species. These studies include longitudinal on-farm studies and experimental animal-group studies that include a control group.

An example of how NARMS data have been used in a risk assessment model was the use of the data to indicate a rise in resistance of *Campylobacter* to the antimicrobial fluoroquinolone. That finding prompted research designed to directly measure the impact of fluoroquinolone use in broilers, which are a major reservoir of *Campylobacter*. This type of targeted

(Continued, next page)

Role of NARMS in Assessing Risk... *(Continued)*

research is a byproduct of the NARMS program and is needed to fully evaluate NARMS phenotypic data.

NARMS data and antimicrobial drug applications

In 2003, CVM updated its regulatory policy to include a microbial food safety assessment for all new antimicrobial products proposed for use in food-producing animals. FDA published Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern" (*http://www.fda.gov/cvm/Guidance/published.htm*). This guidance, which provides a framework for approaching microbial food safety assessments in an organized manner, does not cause FDA to limit its consideration with regard to microbial food safety. In accordance with the Federal Food, Drug, and Cosmetic Act, the Agency's decision regarding whether to approve a new animal drug application is driven by factors that include: (1) whether the application includes adequate tests to determine whether the drug is safe, (2) whether the results of these tests show the drug is unsafe or fails to demonstrate the drug is safe, or (3) whether, based on information either in the application or otherwise available to the Agency, there is sufficient information to determine that the drug is safe.

The guidance contains non-binding recommendations to sponsors concerning the approval of antimicrobials for food-producing animals. It provides sponsors of antimicrobial new animal drugs with an example of what would address FDA's concerns about emergence and selection of antimicrobial resistant bacteria in or on food-producing animals as a result of the use of a sponsor's drug product in those target animals. FDA is concerned that public health may be adversely affected, as humans are exposed to foodborne bacteria that are pathogens to human and that become resistant to antimicrobials used to treat illness in humans.

The Guidance for Industry is comprised of subparts which, when considered as a whole, constitute a microbial food safety assessment.

The first part of the assessment is a hazard characterization. Presenting the Agency with a hazard characterization is a good choice for sponsors to consider if they have a product that has been previously approved and they are proposing only minor changes to the conditions of use (or original conditions of approval), such as adding a new claim, defining a bacterial organism in the indication, adding a new target animal class, or making minor changes to excipients.

The hazard characterization normally contains basic information on:

- Specifics of the drug (chemical class, structure, mechanism of action, spectrum of activity, etc.);
- Antimicrobial resistance information (species and strains of bacteria of public health concern, and phenotypic/genotypic resistance characteristics associated with the identified bacteria of public health concern); and
- Data gaps that might be of interest to the overall picture and the extent to which they are relevant.

Full microbial food safety assessment

Release Assessment: If the hazard characterization presented is not sufficient or substantial gaps in the data exist between what was presented by the sponsor and what FDA may have concerns about, a full microbial food safety assessment (i.e., qualitative risk assessment) may be required. The assessment is composed of three parts. The first part of the full microbial food safety assessment is a sub-assessment referred to as the release assessment.

Here, sponsors will provide information from a variety of sources to answer more in-depth questions, compared to the hazard characterization, about their product, including:

- Active/inactive ingredients
- Conditions of use
- Drug description
- Mechanism of action
- Mode of antibacterial action
- Spectrum of activity
- Specific susceptibility data
- Pharmacokinetics and pharmacodynamics of the drug
- Additional effects of the drug (first-exposure effects, post-antibiotic effects, sub-minimum inhibitory concentrations effects, concentration and/or time-dependent effects, etc.).

Information on resistance mechanisms and genetics, such as known mechanism(s) of resistance in animal and human pathogens (e.g., antimicrobial inactivation, alteration of the drug target, reduced uptake, efflux of the antimicrobial drug, etc.), and the transmissibility of resistance determinants (e.g., plasmid-mediated or chromosomal; present on transposon, integron, or phage) should be supplied.

(Continued, next page)

Role of NARMS in Assessing Risk... *(Continued)*

The occurrence and rate of transfer of resistance determinants should also be described if known.

Sponsors should characterize the relative magnitude of selection pressure for resistance that may exist for their particular drug, including information on other antimicrobials that may co-select for resistance, and information regarding cross-resistance to other antimicrobial drugs approved in veterinary and human medicine.

Finally, information on baseline prevalence of resistance should be provided.

Sponsors should describe available epidemiological data on existing resistance to their drug and/or related drugs in target pathogens and commensal intestinal flora. These data may be newly generated or come from existing sources, such as current literature or other reliable surveillance sources, such as NARMS.

NARMS data can be used especially in the release assessment, since NARMS monitors changes in antimicrobial drug susceptibilities among enteric organisms of public health concern. Because NARMS provides a national source of enteric bacterial isolates that could be used for research on the characterization of molecular mechanisms of resistance, and for studying mobile gene elements, sponsors of new animal antimicrobial drugs may be able to partner with NARMS researchers to identify resistance traits relevant to their specific drug product. Through this partnership, they also could better understand how their drug product will affect resistance in such a pool of readily available organisms, giving them an idea of what resistance impact may occur should their product be approved and used in food-producing animals.

Exposure Assessment: Following the release assessment is the exposure assessment, the second part. It describes the likelihood of human exposure through animal-derived food products to foodborne bacteria of human health concern. Evaluating new animal antimicrobial drug microbial food safety relative to the most significant exposure pathway (i.e., foodborne pathway) is the best way to qualitatively assess the risk of antimicrobial drug use in food-producing animals.

Contemporary survey data about a contamination (low, medium, or high) of a food commodity associated with the target animal species/class and the level of consumption (low, medium, or high) may support a qualitative ranking of the probability of human exposure to the given bacteria via a particular food commodity. Retail meat monitoring done through NARMS provides data at a point of exposure close to consumers.

When combined with data from slaughter plants and on-farm studies, these contemporary survey data provide insight into the prevalence of antimicrobial resistance in foodborne pathogens originating from food-producing animals.

The NARMS retail meat program can be especially helpful in determining exposure assessments. NARMS retail meat data might be used to address concerns about exposure in areas where high contamination and high consumption of food products from target animals present a particular level of risk. In addition, it is difficult to track the spread of foodborne pathogens in or on treated animals that are still on the farm, as they are processed into food, and eventually as the food products arrive at the retail point of sale. NARMS retail meat data may offer compelling insight on the extent to which pathogens are presented to humans in the retail setting.

Consequence Assessment: The consequence assessment, the third part of the microbial food safety assessment, recognizes that some antimicrobials are more important for treating human infections. Thus, the use of a proposed new animal antimicrobial drug is compared against a ranking of the same or similar antimicrobial drugs used in human medicine. Human antimicrobials are ranked by FDA with respect to importance to human medicine and determined to be "important," "highly important," or "critically important." These rankings were established based on a set

(Continued, next page)

Major NARMS Goals

The National Antimicrobial Resistance Monitoring System has four major goals.

They are to:

- Provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in enteric organisms from the human and animal populations;
- Respond to unusual or high levels of bacterial drug resistance in humans, animals, and retail meats in order to contain or mitigate resistance dissemination;
- Design follow-up epidemiology and research studies to better understand the emergence and transfer of antimicrobial drug resistance; and
- Assist FDA in decision-making processes for approving safe and effective drugs, as well as promoting prudent and judicious use of antimicrobials.

Role of NARMS in Assessing Risk... *(Continued)*

of criteria developed with input from the animal health industry, farmers, consumers, human medical community, and others. Sponsors can refer to Appendix A of the Guidance for Industry to see where their drug product(s) will fall on the importance continuum.

Integration, risk ranking, and risk mitigation

Outcomes from the release, exposure, and consequence assessments are integrated to derive an overall risk ranking of low, medium, or high. This risk ranking corresponds to default (but flexible) risk mitigation strategies under categories that describe the safest conditions of use possible for a drug (or drug class) in target animals with respect to antimicrobial resistance emergence and selection.

One of the tenets of the categorization is a need for active post-approval monitoring for resistance. The use of NARMS, which tracks antimicrobial agents representing several antimicrobial classes, is a readily available mitigation step. Furthermore, NARMS can easily be updated to include new antimicrobial drugs or to give priority to screening for antimicrobial drugs of particular interest as related to a particular approval.

Conclusion

Sponsors of antimicrobial new animal drugs can follow the outline set forth in the Guidance for Industry to gauge how their product might be regarded as a contributor to antimicrobial resistance among pathogens of interest (and, therefore, its contribution to the hazard), as well as the risk (as a probability of occurrence of the hazard) it might present to public health. This determination is based on product characteristics, its particular conditions of use in target food animals, and the importance of the subject drug (or drugs in the same class) in human medicine.

Further, a sponsor can use the guidance to anticipate possible risk management mitigations that could be applied to their product as safeguards against resistance selection.

The qualitative risk assessment in FDA's Guidance for Industry outlines one approach for addressing concerns about antimicrobial resistance as applicable to original or supplemental new animal antimicrobial drug applications in food-producing animals. Data gathered in NARMS can be used to help determine the public health burden posed by resistant pathogens, measure the impact of interventions, and to make informed medical and regulatory decisions.

In addition, the development of risk assessments and mathematical models for foodborne disease epidemiology is important for prioritizing the use of limited public health resources. NARMS surveillance and research activities are designed to supply the data needed to inform and prioritize science-based approaches to ensuring food safety, and to minimize public health concerns with regards to antimicrobial use in food animals.

Regulatory Activities *(Continued)*

treatment records and failing to segregate treated animals to ensure that drugs had been used only as directed and that appropriate withdrawal times had been observed prior to offering an animal for slaughter for human food.

Dennis D. Luce, owner of 4D Cattle, Fort Sumner, NM, has received a WARNING LETTER from FDA for violations of the adulteration provisions of the FFDCA. Specifically, the firm offered a Holstein steer for sale as food that contained 18.6 ppm tilmicosin in the liver tissue and 7.5 ppm of the drug in the muscle tissue. In addition, the USDA inspection also revealed the presence of phenylbutazone in the kidney tissue of the animal. FDA has set a tolerance for tilmicosin at 1.2 ppm in the liver tissue of cattle and 0.1 ppm in the muscle tissue of cattle (21 CFR 556.735). No tolerance has been established for residues of phenylbutazone in the edible tissues of cattle. The presence of these levels of these drugs rendered the animal adulterated under Section 402(a) of the FFDCA. In addition, the WARNING LETTER cited the firm for violation of the safety provision of Section 512(a) of the FFDCA and the adulteration provisions of Section 501(a)(5) of the FFDCA.

FDA issued a WARNING LETTER to Jerry A. Settles, majority owner and partner of the Del Oro Dairy, Anthony, NM, for violations of the adulteration provisions of the FFDCA. Specifically, the firm offered for sale as food a Holstein dairy cow that was found to contain 8.99 ppm sulfadimethoxine in the muscle tissue and 11.8 ppm of the drug in the liver tissue. FDA has set a tolerance of this drug at 0.1 ppm in the edible tissues of cattle (21 CFR 556.640). Exceeding the tolerances constituted a violation of Section 402(a). In addition, the firm was found to lack an adequate system to ensure that animals medicated by it have been withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from

(Continued, next page)

Regulatory Activities *(Continued)*

edible tissues. For example, the firm failed to maintain and review complete treatment records and it lacked an adequate inventory system for determining the quantities of drugs used to medicate its animals.

Jason Flores, owner of the Dan Dee Dairy, LLC, in Dexter, NM, also received a WARNING LETTER from FDA for violations of Section 402(a) of the FFDCA. The firm sold a dairy cow for slaughter as food that contained the drug flunixin at 1.06 ppm in the liver tissue of the animal. FDA has set a tolerance for flunixin at 0.125 ppm in such tissue (21 CFR 556.286). In addition, the firm adulterated flunixin within the meaning of section 501(a) of the FFDCA when it failed to use the drug in conformance with the approved labeling. Extralabel use is permitted only if the use is by or on the lawful order of a licensed veterinarian within the context of a valid veterinarian-client-patient relationship and in compliance with the requirements of 21 CFR Part 530. The firm administered flunixin without following the withdrawal period set forth in the approved labeling and did so without the supervision of a licensed veterinarian, in violation of 21 CFR Part 530. Because the extralabel use of this drug did not comply, the drug was unsafe under section 512(a) of the FFDCA and adulterated within the meaning of section 501(a).

Daniel VanGrouw and Sam Adams, owner and manger, respectively, of the Simco Dairy in Boise, ID, have received a WARNING LETTER from FDA for violations of the adulteration provisions of the FFDCA involving four cows. Specifically, the dairy sold a cow for slaughter as food that was found to have residues of penicillin at 1.36 ppm in the kidney and 0.07 ppm in the liver. A second cow contained residues of penicillin at 0.29 ppm in the kidney, and a third cow contained penicillin residues of 1.34 ppm in the kidney and 0.09 ppm in the liver. A tolerance of 0.05 ppm has been established by FDA for residues of this drug in the uncooked edible tissues of cattle (21 CFR 556.510). A fourth cow contained residues of the drug flunixin at 0.163 ppm in the liver. FDA has set a tolerance of 0.125 ppm for flunixin in the liver tissue of cattle (21 CFR 556.286(b)(1)(i)). Violations of FDA's extralabel use provisions for drugs were also cited in the WARNING LETTER.

A WARNING LETTER was issued by FDA to Donald J. Moisan, owner of the Moisan Dairy, Salem, OR, for violations of the adulteration provisions of the FFDCA. Specifically, an animal was offered for slaughter as food that contained residues of the drug sulfadimethoxine in the liver tissue at 7.27 ppm and in the muscle tissue at 1.60 ppm. The kidney tissue was found to contain residues of penicillin at 2.22 ppm. A tolerance of 0.1 ppm has been established for residues of sulfadimethoxine (21 CFR 556.640(b)(1)) in the uncooked edible tissues of cattle, and a tolerance of 0.05 ppm has been established for residues of penicillin in the uncooked edible tissues of cattle (21 CFR 556.510(a)). The excess drug levels rendered the food adulterated under Section 402(a) of the FFDCA. Among other violations, the firm was also found to have provided a false guaranty in violation of Section 301(h) of the FFDCA.

Recalls

A Class I firm-initiated recall is ongoing by Hartz Mountain Corp., Secaucus, NJ, for 2,772 bottles (231 cases) Hartz Vitamin Care for Cats and Kittens distributed nationwide. Surveillance samples collected and analyzed by FDA tested positive for *Salmonella*.

PetEdge, Inc., of Beverly, MA, is carrying out a Class II firm-initiated recall of 25,440 units of its Top Performance Pro-Dental Toothpaste that was marketed nationally and internationally. The reason for the recall is that the toothpaste, which was manufactured in mainland China, was contaminated with diethylene glycol.

A Class II firm-initiated recall of 2,168 cases of cat food under the "Lick Your Chops Healthy Pet Food" label has been completed by Menu Foods, Inc., of Pennsauken, NJ. The products, which were distributed in Pennsylvania and Canada may contain "non-protein nitrogen compounds."

Sergeant's Pet Cat Products, Inc., of Omaha, NE, is conducting a Class III firm-initiated recall of 18,791 of its tropical fish food under the "Atlantis" label. The finished tropical fish food products, which were distributed nationwide and internationally, were found by the Georgia Department of Agriculture and Sergeant's to contain melamine, an unapproved feed additive. The manufacturer was Five Eels Industry Corp. of Taipei, Taiwan.

A Class III firm-initiated recall is ongoing by United Pet Group, Inc., of Cincinnati, OH, for 54,178 units of several pet treats that were imported from China. FDA sampled the treats, and they were positive for melamine. The shipments were placed on hold for redelivery but were erroneously shipped into commerce. Distribution took place in Arizona, California, Florida, Michigan, New Jersey, Texas, and Washington.

Approvals for November-December 2007; January 2008

CVM has published in the *Federal Register* notice of the approval of these New Animal Drug Applications (NADAs)

SIMPLICEF AVIAX II (semduramicin) (NADA 141-281), filed by Phibro Animal Health, Ridgefield Park, NJ. The NADA provides for the use of AVIAX II (semduramicin) Type A medicated article containing semduramicin (as semduramicin sodium biomass) to manufacture Type C medicated broiler chicken feed for the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mitis*. Notice of approval was published January 4, 2008.

(Continued, next page)

Approvals for November 2007 - January 2008 *(Continued)*

CVM has published in the *Federal Register* notice of the approval of these Supplemental New Animal Drug Applications (NADAs)

- CEFA-LAK (cephapirin sodium) and TODAY (cephapirin sodium) Intramammary Infusion (supplements to NADA 97-222), filed by Fort Dodge Animal Health, Fort Dodge, IA. The supplemental NADAs provides for the use of CEFA-LAK (cephapirin sodium) and TODAY (cephapirin sodium) Intramammary Infusion for administering to lactating cows for the treatment of mastitis. Notice of approval was published January 17, 2008.

- PREVICOX (firocoxib) Chewable Tablets (supplement to NADA 141-230), filed by Merial Ltd., Duluth, GA. The supplemental application provides for the veterinary prescription use of firocoxib Chewable Tablets in dogs for the control of post-operative pain and inflammation associated with soft-tissue surgery. Notice of approval was published January 16, 2008.

- PIRSUE (pirilimycin hydrochloride) Sterile Solution (supplement to NADA 141-036), filed by Pharmacia & Upjohn Co., New York, NY. The supplemental NADA provides for the veterinary prescription use of PIRSUE (pirilimycin hydrochloride) Sterile Solution in lactating dairy cattle for the treatment of mastitis. The supplement extends the dosage regimen to daily treatment for up to 8 days. Notice of approval was published January 4, 2008.

- OPTAFLEXX (ractopamine hydrochloride), MGA (melengestrol acetate), and RUMENSIN (monensin USP) (supplement to NADA 141-234), filed by Elanco Animal Health, Indianapolis, IN. The supplemental NADA provides for the use of OPTAFLEXX (ractopamine hydrochloride), MGA (melengestrol acetate), and RUMENSIN (monensin USP) Type A medicated articles to make dry and liquid three-way combination Type C medicated feeds used for increased rate of weight gain, improved feed efficiency, and increased carcass leanness; for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*; and for suppression of estrus (heat) in heifers fed in confinement for slaughter during the last 28 to 42 days on feed. The supplemental NADA provides for an increased level of monensin. Notice of approval was published December 13, 2007.

- PENNOX (oxytetracycline) (supplement to NADA 138-938), filed by Pennfield Oil Co., Omaha, NE. The supplemental NADA provides for the use of PENNOX (oxytetracycline) Type A medicated articles used for making medicated feeds for the treatment of various bacterial diseases of livestock and fish. The supplemental NADA provides for a zero-day withdrawal time prior to slaughter when Type C medicated feeds containing oxytetracycline are fed to turkeys or swine and for minor label revisions. Notice of approval was published December 13, 2007.

- GALLIMYCIN-100 (erythromycin) Injection (supplement to NADA 12-123), filed by Cross Vetpharm Ltd., Dublin, Ireland. The supplemental NADA provides for the use of a 100 mg/mL strength of GALLIMYCIN-100 (erythromycin) injectable solution in cattle for the treatment of bovine respiratory disease. Notice of approval was published December 7, 2007.

- RUMENSIN (monensin USP) and TYLAN (tylosin phosphate) (supplement to NADA 104-646), filed by Elanco Animal Health, Indianapolis, IN. The supplemental NADA provides for the use of RUMENSIN (monensin USP) and TYLAN (tylosin phosphate) Type A medicated articles to make dry and liquid two-way combination medicated feeds for cattle fed in confinement for slaughter. The supplemental NADA provides for an increased level of monensin in combination Type B and Type C medicated feeds and a revision to bacterial pathogen nomenclature. Notice of approval was published December 5, 2007.

- RUMENSIN 80 (monensin) (supplement to NADA 95-735), filed by Elanco Animal Health, Indianapolis, IN. the supplemental NADA provides for use of RUMENSIN 80 (monensin) Type A medicated articles, specifically removing the requirement for 30-day expiration on labeling of monensin Type C medicated feeds for several classes of cattle and goats. Notice of approval was published December 5, 2007.

- SAFE-GUARD (fenbendazole) (NADA 131-675), filed by Intervet Inc., Millsboro, DE. SAFE-GUARD (fenbendazole) 20% Type A medicated article is approved to formulate Type B and Type C medicated horse feeds. The approved supplemental NADA provides for a revised food safety warning on the labeling. Notice of approval was published November 27, 2007.

- AQUAFLOR (florfenicol) (NADA 141-246), filed by Schering-Plough Animal Health Corp., Summit, NJ. The approved supplemental NADA provides for the use of AQUAFLOR (florfenicol), a Type A medicated article, by veterinary feed directive to formulate Type C medicated feed for the control of mortality in freshwater-reared salmonids due to furunculosis with *Aeromonas salmonicida*. Notice of approval was published November 26, 2007.

- OPTAFLEXX (ractopamine hydrochloride) and RUMENSIN (monensin USP) (NADA 141-225), filed by Elanco Animal Health, a Division of Eli Lilly & Co., Indianapolis, IN. The approved supplemental NADA provides for the use of OPTAFLEXX (ractopamine hydrochloride) and RUMENSIN (monensin USP) Type A medicated articles to make dry and liquid two-way combination medicated feeds for cattle fed in confinement for slaughter. The supplemental NADA provides for an increased level of monensin in combination Type B and Type C medicated feeds. Notice of approval was published November 23, 2007.

- AUREOMYCIN (chlortetracycline) Soluble Powder Concentrate (NADA 65-440), filed by Fort Dodge Animal Health, Fort Dodge, IA. The approved supplemental NADA provides label revisions for the use of AUREOMYCIN (chlortetracycline)

(Continued, next page)

Approvals for November 2007 - January 2008 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

Soluble Powder Concentrate. The product is approved for oral use in medicated drinking water of chickens, growing turkeys, swine, calves, beef cattle, and nonlactating dairy cattle for the control and/or treatment of various bacterial diseases. Notice of approval was published November 14, 2007.

OPTAFLEXX (ractopamine hydrochloride), RUMENSIN (monensin USP), and TYLAN (tylosin phosphate) (NADA 141-22), filed by Elanco Animal Health, Indianapolis, IN. The approved supplemental NADA provides for the use of OPTAFLEXX, RUMENSIN, and TYLAN Type A medicated articles to make dry and liquid three-way combination medicated feeds for cattle fed in confinement for slaughter. The supplemental NADA provides for an increased level of monensin in combination Type C medicated feeds and a revision to bacterial pathogen nomenclature. Notice of approval was published November 6, 2007.

CVM has published in the *Federal Register* notice of the approval of these Abbreviated New Animal Drug Applications (ANADAs)

CLINDAROBE (clindamycin hydrochloride) Capsules (ANADA 200-383), filed by Novapharm Ltd., Toronto, Ontario, Canada. The ANADA provides for the veterinary prescription use of CLINDAROBE (clindamycin hydrochloride) Capsules in dogs for the treatment of various infections due to susceptible bacterial pathogens. Novopharm's CLINDAROBE Capsules are approved as a generic copy of Pharmacia & Upjohn Company's ANTIROBE Capsules, approved under NADA 120-161. Notice of approval was published January 24, 2008.

VETPROFEN (carprofen) Caplets (ANADA 200-397), filed by Belcher Pharmaceuticals, Largo, FL. The ANADA provides for veterinary prescription use in dogs for the relief of pain and inflammation associated with osteoarthritis, and for the control of post-operative pain associated with soft tissue and orthopedic surgeries. VETPROFEN Caplets are approved as a generic copy of RIMADYL Caplets, sponsored by Pfizer, Inc., under NADA 141-053. Notice of approval was published December 5, 2007.

CVM has published in the *Federal Register* notice of the approval of these Supplemental Abbreviated New Animal Drug Applications (ANADAs)

FLUNIXIN INJECTION (ANADA 200-308), filed by Norbrook Laboratories, Newry, Northern Ireland. The approved supplemental ANADA provides for the veterinary prescription use of FLUNIXIN INJECTION intravenously in lactating dairy cattle for the control of pyrexia associated with acute bovine mastitis. Notice of approval was published January 16, 2008.

NOROMECTIN (ivermectin) Injection (ANADA 200-437), filed by Norbrook Laboratories, Newry, Northern Ireland. The approved supplemental ANADA for Noromectin (ivermectin) Injection for Cattle and Swine adds claims for persistent effectiveness against various species of external and internal parasites of cattle. These include gastrointestinal roundworms, lungworms, grubs, sucking lice, and mange mites. Notice of approval was published November 7, 2007.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
HFV-12
Rockville MD 20857

Official Business
Penalty for Private Use $300

PRESORTED STANDARD
POSTAGE AND FEES PAID
TEMPLE HILLS, MD
PERMIT NO. 4004

Use of funds to print the **FDA Veterinarian** has been approved by the Office of Management and Budget.

08-0362