FDA VETERINARIAN
Center for Veterinary Medicine
September/October 2003 Vol. XVIII, No. V

Cloning: Revolution or Evolution in Animal Production?

by Linda Bren

This article appeared in the May/June issue of the ***FDA Consumer****.*

Full Flush is a celebrity. No one asks for his autograph, but they do ask for his progeny. Named for a winning poker hand, the aging grand champion bull can't meet the demand of all the cattle ranchers who want more like him. But the bull's clones may keep his legacy alive.

Full Flush's five clones "were as normal and healthy as any calves I've ever raised," says rancher and veterinarian Donald Coover of Galesburg, Kan., who bottle-fed the young calves and raised them for the first six months of their lives. The calves, born in 2001, will soon be ready to propagate herds of high-quality beef cattle.

To the uninitiated, animal cloning may conjure up visions of strange, robot-like creatures, but real clones are far from this science-fiction fallacy. "This is just an assisted reproductive technology," says Mark Westhusin, Ph.D., director of the Reproductive Sciences Laboratory at Texas A&M University's College of Veterinary Medicine. "We're not trying to resurrect animals or get animals back."

"Clones are biological copies of normal animals," says Larisa Rudenko, Ph.D., a molecular biologist and risk assessor in the Food and Drug Administration's Center for Veterinary Medicine (CVM). "In theory, they're pretty close to identical twins of an adult animal."

Although the technology to clone farm animals was developed more than 20 years ago, today's method of cloning, somatic cell nuclear transfer (SCNT), has been around only since 1996. Coover estimates that only a couple hundred of the 100 million cattle in the United States are SCNT clones. And you won't find meat or milk from SCNT cloned animals in your supermarket yet—the FDA has asked companies that clone animals not to introduce any of them, their offspring, or their food products into human or animal food until the agency has evaluated the safety of these products. The companies are cooperating, says Stephen Sundlof, D.V.M., Ph.D., director of the FDA's CVM. "And we're being very diligent to make sure if this new

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Full Flush

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

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technology makes it to the marketplace, that it's safe for people to eat."

It's unlikely that you will eat a cloned animal anytime soon. At a cost of about $20,000 each to produce, clones are used for breeding—not for food. But some scientists and farmers are looking at the descendants of cloned cattle, pigs, goats and sheep as potential sources for food and clothing, if the FDA gives the OK.

Mandated with protecting the nation's food supply and animal health, the FDA is working to set a policy on cloned animals, based on the best available science. "We do not want these products on the market until there has been a thoughtful, thorough and deliberate evaluation of the issues," says Sundlof. "We want to make sure that the public is clearly informed and that they have had a chance to participate in the process."

"We do not want these products on the market until there has been a thoughtful, thorough and deliberate evaluation of the issues," says [CVM Director] Sundlof. "We want to make sure that the public is clearly informed and that they have had a chance to participate in the process."

The Cloning Process

Early methods of cloning in the 1970s involved a technology called embryo splitting, or blastomere separation. Embryos were split into several cells and then implanted into a surrogate mother for growth and development. But there were a limited number of splits that could be made, and only a few clones could be produced from one egg. The characteristics of the clone were also unpredictable because scientists were cloning from an embryo whose traits could not be predicted.

The practice of cloning took on new meaning in 1996 with the birth of Dolly the sheep, the world's first mammal cloned from an adult cell. Dolly was produced using SCNT technology. Since the cloning of Dolly, this technology has been used to clone cattle, mice, goats, pigs, rabbits, and even a cat. Unlike the embryo splitting method, in theory, SCNT can be used to make an unlimited number of copies of one animal.

The SCNT process starts with an unfertilized egg, or oocyte. Scientists remove the oocyte's nucleus, which contains the egg's genes, or hereditary "instructions." What remains after removal of the nucleus is a cell that contains nutrients essential for embryo development and other cellular machinery waiting for a new set of instructions.

A somatic cell from the animal to be cloned—or in some cases, just the cell's nucleus—is cultured in an incubator and then injected under the coating of the unfertilized oocyte. (Somatic cells are any cells of the body except sperm and eggs.) Stimulated by a mild electrical pulse, the oocyte cytoplasm (everything in the cell but the nucleus) and the genetic material from the donated somatic cell combine. If fusion is successful, the resulting fused cell divides just as if it were a fertilized egg and produces an embryo. The embryo is placed in the uterus of a surrogate mother and, if development proceeds normally, an animal clone is born.

But there's a tricky part to this process, says Rudenko. The nucleus of the adult cell is specialized, or differentiated, for a particular function. "The nucleus has matured to a point where its instructions are 'locked away' in a configuration specific to the job that the cell is intended to perform," says Rudenko. "For example, a muscle cell has a different job from a liver cell, and it has a different set of instructions available to it. The complicated part of cloning that we don't fully understand is how those instructions get reset."

The unlocking and resetting of instructions without making changes to the genetic code is called epigenetic reprogramming. This process allows the cell to develop into a new organism instead of continuing to do its old specified cellular functions. And it's the epigenetic reprogramming that scientists haven't yet mastered and that accounts for frequent cloning failures.

Steven Stice, Ph.D., explains epigenetics as the propensity for different outcomes from identical DNA sequences. An example of an epigenetic effect in normal human birth is the different fingerprint patterns of identical twins, says Stice, a professor in the Animal and Dairy Science Department at the University of Georgia and chief scientific officer for ProLinia Inc., a livestock cloning company in Athens, Ga. Epigenetic changes are not unique to cloning but are more noticeable in clones, Stice adds. "Everything from in vitro fertilization to artificial insemination can have epigenetic effects."

Why Clone?

Proponents of livestock cloning see it benefiting consumers, producers, animals and the environment.

"The consumer is looking for a nutritious and wholesome product provided to them in a repeatable and reliable

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FDA VETERINARIAN

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Published bi-monthly.

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Photo by Christy Collins/Collins Cattle Services

Clones of Full Flush

manner and produced in a humane and ethical way," says Coover, who also owns and manages SEK Genetics Inc., a beef cattle semen distribution company. "If a consumer spends $30 on a steak dinner at a restaurant, they expect a great steak, but don't always get it."

For farmers whose livelihoods depend on selling high-quality meat and dairy products, cloning can offer a tremendous advantage, says Coover. It gives them the ability to preserve and extend proven, superior genetics. They can select and propagate the best animals—beef cattle that are fast-growing, have lean but tender meat, and are disease-resistant; dairy cows and goats that give lots of milk; and sheep that produce high-quality wool. Through cloning, it would be possible to predict the characteristics of each animal, rather than taking the chance that sexual reproduction and its gene reshuffling provide.

Coover compares the process of identifying a superior animal to spinning a giant roulette wheel. "Sometimes you win, sometimes you lose, and sometimes you hit the jackpot." But a producer cannot tell if he's hit the jackpot with a young animal. "It's like trying to identify the school kid in the second grade who is going to grow up to solve the riddle of cancer," says Coover. "A rancher may think he has a good bull, but that bull has to sire calves, the calves have to mature and produce calves of their own, and this has to occur for several generations to know that it's not a fluke. By that time, the bull is dead and gone, and its genetics are lost to the industry." Through SCNT cloning, even deceased animals can be cloned if a tissue sample is preserved in life or within a short time after death.

Cloning has the potential to improve the welfare of farm animals by eliminating pain and suffering from disease. "From time to time, in nature, you find a naturally disease-resistant animal," says Rudenko. "You can expand that genome through cloning, and then breed that resistance into the overall population and help eliminate major diseases in livestock."

Cloning can reduce the number of unwanted animals, such as veal calves, says Ray Page, chief scientific officer and biomedical engineer at Cyagra, a livestock cloning company. Veal calves are commonly surplus male offspring from dairy cows. Since the males don't produce milk, they are not as useful to the dairy industry and are turned into veal calves. Cloning can ensure the creation of more female offspring for dairy production.

An environmental benefit could result from cloning grass-fed instead of grain-fed animals. Grain-fed animals are known to be better tasting and more tender, but once in a while, a high-quality grass-fed animal comes along. "If we can move our cattle-raising from a grain economy to a grass-fed economy, we can make food more efficiently and there are benefits to us as a society," says John Matheson, a toxicologist and environmentalist who serves as a senior regulatory review scientist for biotechnology in CVM. Grass is a soil-building crop. In addition to reducing erosion, grass does not need the quantities of fertilizers and pesticides required by grain. And because forage is cheaper than grain, production savings can be passed on to consumers.

"Cloning can help spread the best genetics over larger populations of animals," says Stice. When farm animals are cloned, genetic diversity may be reduced, but cloning can also be a tool to preserve rare genetics in livestock and, potentially, wild animals. Stice encourages zoos and wildlife refuges to preserve the tissue of endangered species in the hopes that technology in the theoretical stage today can be developed to regenerate these species in the future.

Cloning Concerns and the FDA's Role

While cloning proponents see enormous capabilities for the technology, cloning critics have concerns on a number of levels. Social, ethical and religious convictions all weigh in to make people wary of cloning. Some find it hard to separate animal cloning from human cloning. But cloning scientists view animal cloning on a continuum of reproductive technology. Improving breeding practices in the hopes that offspring will be improved has been going on for thousands of years. Arab chieftains were using artificial insemination in horse breeding as early as the 14th century, according to historians.

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Cloning: Revolution or Evolution . . . *(Continued)*

"There's always been a fear of new technology," says Matheson, who notes that cloning animals is not a precursor to cloning humans. "We already know more about reproduction in humans than in any other species, so there's no learning curve to be gained in cloning cows."

Matheson explains that the FDA's role is to look at the safety aspects of cloning based on the best available science. The FDA needs to answer an important question to help it develop its regulatory approach to animal cloning, he says. "Is this risky new technology that endangers animals and our food supply, or is this just another small step in the evolution of food production technology?" To answer this question, the FDA is gathering more data.

The FDA commissioned the National Academy of Sciences (NAS) to identify and prioritize any safety concerns that bioengineered and cloned animals might present to food, animals and the environment.

After consulting with pioneers in the field of cloning and holding a public workshop, the NAS published its report, *Animal Biotechnology: Science-Based Concerns*, in August 2002. According to the report, "There is no current evidence that food products derived from adult somatic cell clones or their progeny present a food safety concern." The report recommends collecting additional information about food composition to confirm that these food products are, in fact, safe. Food should be analyzed for such essential ingredients as amino acids, vitamins and minerals and to make sure cloned animal products don't differ from those of normal animals in ways that might affect human health.

But this analysis is not as easy as you might think, says Matheson. "We don't know what the composition of 'normal milk' is. It may all taste the same from the market, but it can vary a lot in each individual animal depending on its age, what it eats, and the time of lactation. Qualitatively, most of the same ingredients are always present, but quantitatively, their actual concentration varies from animal to animal." This may be true for meat as well since each animal is different just like each human is different. "Even though we think of a pork chop as a pork chop and a steak as a steak, they're each a little bit different from one another in chemical composition," adds Matheson.

The NAS report cited environmental concerns regarding genetically engineered fish and other animals that could escape into the environment, reproduce, or compete successfully for food and mates with wild animals. But this concern does not extend to cloned domesticated animals, since cattle and other livestock generally do not run wild and have no wild counterparts in the United States with which to interbreed.

Cloning may someday reduce the number of animals needed for food and fiber production, according to the report, but could also have adverse effects on animal welfare. Calves and lambs produced through cloning tend to have higher birth weights and longer gestation periods, which may lead to difficult births. Repeated exposure of individual animals to invasive procedures to harvest oocytes for SCNT is likely to cause pain and distress. In addition, the survival rate of cloned fetuses is low, and some survivors have health problems such as heart and lung disease.

The FDA is developing two risk assessments: one describing the potential risks, if any, of consuming food products from animal clones and their offspring, and the other describing health risks to animal clones and their offspring.

Speculation surrounds the death of Dolly the sheep. Dolly had been diagnosed with arthritis in her hind limbs when she was about 4 years old. In February 2003, she was euthanized at the age of 8 because of a degenerative lung condition most probably caused by a virus. Critics blame cloning for Dolly's lung disease and her arthritis. But others attribute her health problems to being overweight and to becoming infected with a virus present in the barn in which she was kept.

Low rates of success are inherent in any new technology, says Page. "But the people doing this are becoming better technicians. We're making improvements in the way we handle cells and embryos. Efficiency rates continue to improve year after year, and more of the embryos are surviving to term and more of the calves are healthy."

The Humane Society of the United States (HSUS) has asked the FDA to ban sales of products from cloned farm animals and their offspring because of "serious concerns about the health and welfare of cloned animals."

"We condemn cloning as yet another move away from regarding animals as animals, and yet another development that will favor large corporations over small ones," says Michael Appleby, Ph.D., HSUS vice president for farm animals and sustainable agriculture. The HSUS commends the FDA for commissioning the NAS report and requesting that food from cloned animals not enter the marketplace. "These measures show an appropriate, precautionary approach," says Appleby, "and we trust the FDA will further this by putting more weight on the animal safety issues outlined in the report."

The NAS's job was to identify the potential risks of cloning; now the FDA is studying those risks to determine how to manage them. The FDA is developing two risk assessments: one describing the potential risks, if any, of consuming food products from animal clones and their offspring, and the other describing health risks to animal clones and their offspring. The FDA will use these assessments to develop an

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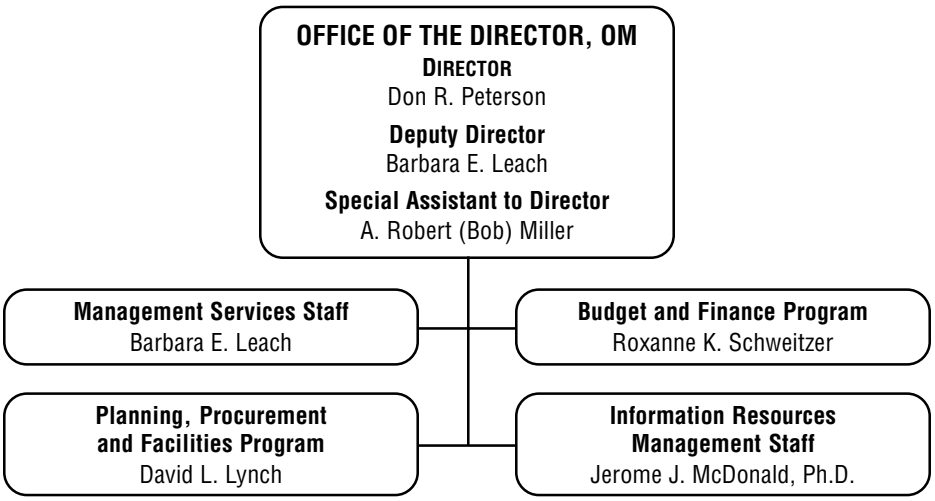
Office of Management (OM) Reorganizes

CVM has announced the reorganization of the Center's Office of Management (OM), formerly known as the Office of Management and Communications (OMAC). The Communications Staff, previously a part of the OM, was realigned under the immediate Office of the Director, reporting to the Associate Director, Executive Programs.

Don Peterson, Director of OM, said the purpose of the OM reorganization is to "accommodate the Agency's consolidation of many administrative services and to more efficiently organize around like functions." Mr. David Lynch will supervise the newly organized Planning, Procurement and Facilities Program and Mrs. Roxanne Schweitzer will supervise the Budget and Finance Program.

Another adjustment is a title change for the former Administrative Staff. It is now the Management Services Staff, supervised by Mrs. Barbara Leach, who also serves as Deputy Director, OM. The CVM Staff College is located under the Management Services Staff and lead by Mrs. Melissa Starinsky. The structure of the Information Resources Management Staff, supervised by Dr. Jerome McDonald, remains unchanged.

The new organizational chart follows:



Cloning: Rovolution or Evolution . . . *(Continued)*

appropriate science-based regulatory approach, in the form of policy or guidance for industry, to manage any food and animal health risks. The public will have the opportunity to comment on this guidance, planned for release by the end of 2003.

In its commitment to a transparent process, CVM gathered together food producers and food consumers to share their perspectives on bioengineered and cloned animals at a three-day public workshop. Held in Dallas in September 2002, the workshop was co-sponsored by the Pew Initiative on Food and Biotechnology, an independent source of information on agricultural biotechnology.

CVM will continue to inform the public as it moves toward a decision on the type of regulatory structure that will be needed for cloned animals. "The public will be well informed and nothing is going to happen that they won't know about," says Sundlof.

Cloning versus Transgenics

Cloned animals and transgenic animals are sometimes mistaken to be the same, but they are different, says Larisa Rudenko, Ph.D., a molecular biologist in the Food and Drug Administration's Center for Veterinary Medicine (CVM).

Transgenic animals or plants are produced by adding or removing genes, or by altering the expression of their existing genes. This process can involve genetic information taken from different species or created in DNA synthesizing machines. When a gene for insulin, for example, is inserted into a goat, the animal could produce insulin in its milk, which would then be purified into an injectable form to treat human diabetes. And genes for growth hormone from one fish species transferred into the genome of salmon can cause them to grow rapidly. (See "A New Kind of Fish Story: The Coming of Biotech Animals," January–February 2001 FDA Consumer.)

Cloned animals are produced using bioengineering techniques but are intended to be biological copies of existing animals.

CVM is developing guidance for cloning food production animals. Future guidance for developing transgenic food animals will build on the cloning guidance and further study.

For More Information

The FDA Center for Veterinary Medicine's web site on biotechnology in animals and feeds

- *www.fda.gov/cvm/biotechnology/bioengineered.html*
- The National Academy of Sciences' 2002 report, *Animal Biotechnology: Science Based Concerns*
- *www.nap.edu/catalog/10418.html*
- Presentations from the September 2002 FDA and Pew Initiative on Food and Bio-technology workshop, "Animal Cloning and the Production of Food Products-Perspectives from the Food Chain" *http://pewagbiotech.org/events/0924/*

Linda Bren is a Writer-Editor with the ***FDA Consumer****.*

CVM Conducts Retail Meat Pilot Study

by Dr. Marcia L. Headrick

Foodborne diseases caused by a variety of organisms, including viruses and bacteria, result in an estimated 5,000 human deaths and 76 million illnesses annually in the United States, according to the Centers for Disease Control and Prevention. *Salmonella* and *Campylobacter* are the most commonly reported bacterial causes of foodborne illness.

Although antimicrobial drug therapy is not recommended for most cases of campylobacteriosis or salmonellosis, it may be life-saving for invasive infections. Development of resistance to antimicrobial drugs recommended for treatment of invasive salmonellosis and campylobacteriosis may compromise treatment outcome, resulting in more severe illness. Retail foods such as raw meat may be contaminated with these resistant organisms.

The FDA's Center for Veterinary Medicine (CVM) conducted a pilot study as a part of the National Antimicrobial Resistance Monitoring System – Enteric Bacteria (NARMS) to collect data on the prevalence and antimicrobial drug susceptibility of foodborne bacteria in retail meat. In addition, this study provided the opportunity to develop laboratory methods for the testing of retail meat products and to determine the feasibility of conducting on-going surveillance of retail meats as part of the NARMS program.

National Antimicrobial Resistance Monitoring System – Enteric Bacteria (NARMS)

To track development of antimicrobial drug resistance of foodborne pathogens in humans and animals, the FDA CVM implemented the NARMS program in collaboration with the Centers for Disease Control and Prevention (CDC) National Center for Infectious Diseases and the U.S. Department of Agriculture (USDA).

NARMS was initiated in 1996 and initially monitored changes in antimicrobial susceptibilities of a sentinel organism, *Salmonella,* isolated from human and animal clinical specimens, from carcasses of food-producing animals and animal products at processing, and from on-farm samples. Sampling of retail meats and animal feed ingredients were added to NARMS in 2002. Also, additional foodborne bacterial organisms are now tested.

In 2003, NARMS is monitoring susceptibilities of human, animal, and retail meat isolates of non-typhoid *Salmonella*, *E. coli*, *Campylobacter*, and *Enterococcus* spp. Human isolates of *Salmonella Typhi*, *Listeria*, and *Shigella* are also tested. Human *Vibrio* isolates are being collected and will be tested in the future. Animal feed ingredient samples are tested for the presence of *Salmonella*, *E. coli*, and *Enterococcus* spp.

NARMS includes three laboratory testing-sites, all using comparable laboratory methods including culture, isolation, identification, storage, and susceptibility testing procedures. NARMS laboratory testing is conducted at CDC (human samples), USDA (animal samples), and FDA CVM (retail meat samples). The program's primary goal is to provide descriptive data on the extent and trends over time in antimicrobial drug susceptibility of enteric organisms from human and animal populations.

NARMS also facilitates the identification of resistance in humans and animals as it arises, provides information to veterinarians and physicians on antimicrobial resistance, prolongs the life span of approved drugs by promoting the prudent and judicious use of antimicrobial drugs, aids in antimicrobial resistance research, and serves as a national source of enteric bacterial isolates. In addition, the NARMS isolates are invaluable for diagnostic test development, discovering new genes, characterizing molecular mechanisms associated with resistance, studying mobile gene elements, and assessing virulence and colonization potential of resistant isolates.

Iowa Retail Meat Pilot Study

Prior to implementation of the retail meat component of NARMS, a pilot study was conducted in the State of Iowa to determine the feasibility of, and the laboratory methods required for, testing of retail meat products. Iowa was selected since it was not already submitting foodborne illness associated bacterial isolates to a federal monitoring program. It also has a manageable geographic size and is a food-producing State.

Sample collection for the Iowa Retail Meat Pilot Study began in March 2001 and was completed in June 2002. The study design planned for a total of 50 sample collection trips during the study period. A random sample of 300 of approximately 500 retail groceries located in the State of Iowa (supermarkets or superstores) was selected from the Chain Stores Grocery Guide database (Grocery Manufacturers Association of America). Convenience and health food stores were excluded.

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. . . Retail Meat Pilot Study *(Continued)*

Iowa was divided into five geographic regions with equal numbers of groceries selected in each region. A list of 60 stores from each region was randomly selected and ten routes identified per region, with each route consisting of six stores. At each store, one package each of ground beef, pork chops, ground turkey, and chicken breasts were purchased. A standard form was used to record the type of product, date of collection, store location, use-by date, grade, weight, and cost of the samples. No store or brand identifiers were recorded, however it was noted if the store was part of a chain or a single store and if the meat was a "house" or a commercial brand. Other data collected included route, store number, and sell-by date.

One route (six stores) was sampled most Saturdays, excluding holidays. Collection of samples on a weekly basis was designed to assess the seasonal prevalence of the foodborne enteric organisms studied (*Salmonella*, *Campylobacter*, *Enterococcus* spp. and gram-negative bacteria producing extended spectrum beta-lactamases). Each region was sampled sequentially and the process was repeated 10 times over the study period.

The food specimens were transported on ice and delivered to the FDA/CVM Office of Research (OR) laboratory in Laurel, Maryland, on Sunday evening or early Monday morning. Standard methods from the FDA Bacteriological Analytical Manual (BAM) were used to isolate the bacteria of interest from the food samples. Antimicrobial susceptibility testing of isolates from the Iowa Retail Meat Pilot Study was performed using NARMS program laboratory procedures and National Committee for Clinical Laboratory Standards (NCCLS) guidelines, when available. A total of 981 samples from 263 groceries were collected as part of the Iowa Pilot Study and more than 2,000 bacterial isolates were tested at the CVM OR laboratory. This testing included, but was not limited to, identification of bacterial species, serotyping, determination of genetic relatedness, and assessing the presence of virulence factors.

The goals of the Iowa pilot study were to develop pilot methodologies for a retail meat surveillance component of NARMS, estimate the prevalence of bacterial contamination for four food commodities, determine the antimicrobial drug susceptibility patterns of the bacterial strains obtained from the study, and assess risk factors for contamination of retail foods. An additional goal of the pilot study was to compare the characteristics of *Salmonella* and *Campylobacter* isolated from humans in Iowa with the isolates collected from the retail meat samples collected over the same time period. This comparison is ongoing.

Samples for Retail Meat Study included ground beef, ground turkey, portk chops and chicken breasts.

The results from this study will generate prevalence and antimicrobial drug susceptibility data on foodborne *Salmonella*, *Campylobacter*, *Enterococcus* spp. and Gram-negative bacteria producing extended spectrum beta-lactamases in selected retail meat products in Iowa and help quantify the role contaminated food plays in spreading antibiotic resistant bacteria. Demographic data such as potential risk factors for bacterial contamination including seasonality, sell-by date, cost, geographic distribution, and size of store will also be evaluated for trends. Better understanding of the prevalence of antimicrobial drug-resistant bacteria in food will also facilitate development of strategies to interrupt the spread of antimicrobial drug resistant bacteria via foodborne routes. Once analysis of the data is complete, summary results of the NARMS Iowa Retail Meat Pilot Study will be posted on the FDA/CVM NARMS web page at: *http://www.fda.gov/cvm/index/narms/narms_pg.html*.

Acknowledgements: The contributions of many organizations and individuals were essential for the success of the Iowa Retail Meat Pilot Study. Personnel from the Iowa Department of Public Health, Iowa Hygienic Laboratory, Iowa State University, CVM Division of Epidemiology, CVM Division of Animal and Food Microbiology, CVM Biometrics Review Team, and others worked together to make this study possible.

Dr. Headrick is the FDA/CVM NARMS Coordinator.

FDA Commissioner Visits CVM's Office of Research

On September 5, 2005, FDA Commissioner, Dr. Mark McClellan visited CVM's Office of Research in Laurel, Maryland for a firsthand view of CVM's state-of-the-art facility. Dr. Linda Youngman, Director of the Office of Research (OR), provided a brief introduction of ongoing research efforts, and accompanied Dr. McClellan on the tour.

CVM scientists showed Dr. McClellan an adult steer prepared for a laparoscopic (minimally invasive) surgical approach, similar to so-called "keyhole surgery" in humans, to obtain a small biopsy sample of an internal organ under local anesthesia. The biopsy sample is used to develop an estimate of the drug residue level in edible animal tissue as part of the CVM food safety program. The laparoscopic surgery is performed by veterinarian Dr. Alberto Chiesa, visiting scientist from Spain, who has been trained in this minimally invasive approach to surgery at the University of California and the Ohio State University. He is assisted in the surgery by Dr. Richard Cullison, and Dr. Keesla Moulton, OR staff fellow from Mississippi State University and director of the current research effort to determine tissue-fluid correlations as related to drug residue concentration in meat animals.

Dr. McClellan was given a tour of CVM's Office of Research state-of-the-art aquaculture facility by Dr. Renate Reimschuessel. The facility is approximately 5,000 sq ft. and has specialized facilities for conducting infectious studies, radioactive drug exposures and comprehensive fish surgeries. Species currently being studied include tilapia, rainbow trout, Atlantic salmon, channel catfish, and large mouth bass. In addition, goldfish are being used as models for ornamental species to study fish diseases and their treatments.


Photo by Karen A. Kandra

Dr. Renate Reimschuessel gave Dr. McClellan a tour of OR's aquaculture facility . . .

Photo by Karen A. Kandra

. . . some aquatic specimens seen by Dr. McClellan during his tour.

Research at the facility focuses on both regulatory priorities and the needs of the burgeoning aquaculture industry. The U.S. consumption of aquaculture-reared seafoods continues to grow as wild-caught stocks of fish continue to decrease – thus, the growing need for safe and effective therapies for aquaculture use is evident. CVM's Office of Research's studies include utilizing aquatic animal disease models to facilitate new animal drug efficacy trials and conducting residue depletion studies in multiple fish species to facilitate grouping of species (species

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FDA Commissioner Visits CVM's Office of Research *(Cont.)*

grouping) on the basis of their metabolism of various drug classes. Dr. Shaikh is the study director for OR's species grouping studies.

Dr. McClellan visited the Center for Devices and Radiological Health's Office of Science and Technology (OST), Division of Life Sciences, Laboratory of Preclinical Studies. The Director of the Office, Dr. Larry Kessler, introduced Dr. Marilyn Lightfoote (Director, Division of Life Sciences) and Dr. Melvin Stratmeyer (Director, Health Sciences Branch) and briefly discussed the Office's laboratory-based program and its role in supporting the Center's regulatory work. Dr. Stephen Hilbert presented the regulatory and research components of the heart valve program. Dr. McClellan then proceeded to the OST interventional radiology/cardiology suite where an animal study was in progress. This study is part of a preclinical animal trial designed to address specific regulatory issues associated with emerging medical device technology. It was explained that one spedific aim of the current preclinical animal trial is to evaluate the effect of gender on stent versus angioplasty performance in a swine model of coronary atherosclerosis.

The study team was introduced (Dr. William Pritchard, Dr. John Karanian, Dr. Diane Wray-Cahen, Dr. Stephen Hilbert, Autumn Ashby and Dr. Abii Polycarp) as the Commissioner scrubbed-in to participate in the sterile procedure. Dr. McClellan was directed by Dr. Pritchard to perform a diagnostic angiogram of the swine coronaries and then proceeded to successfully deliver and deploy a coronary stent. The animal was subsequently recovered for future studies.

Following the tours, Dr. Youngman provided a talk for Commissioner McClellan highlighting a few of CVM's ongoing research programs:

- **Microbial Source Tracking (MST) Studies** – used to identify methods by which to determine the animal source of the foodborne pathogens: *Salmonella* and *Campylobacter.*
- **Standardization of Antimicrobial Susceptibility Testing Methods** – necessary to allow comparability of data between testing laboratories, and to provide a means for quality control of testing components and procedures to ensure reliable and repeatable data.
- **Development of Multiresidue Methods for Veterinary Drug Residues** – OR scientists have long recognized the need for radical improvements in the time- and cost-effectiveness of measuring for veterinary drug residues in imported foods. Thus, they developed a two-phase extraction scheme that permits rapid extraction of both organic and aqueous phase drugs. They then developed, and are now optimizing, analytical methods that will permit resolution of 18 different drugs (of 6 different classes) in one analytical run. Use of these methods in ORA laboratories should result in dramatic improvements in the numbers of samples that can ultimately be analyzed.
- **Antibiotic Resistance Patterns of Foodborne Bacterial Pathogens Isolated from Retail Meats** – The project objectives are to gain a better understanding of the contribution our food supply contributes to the dissemination of antimicrobial resistant foodborne bacterial pathogens, especially *Salmonella, Campylobacter*, and *E. coli* in meat and poultry.
- **Development and Validation of Methods to Help Enforce FDA's Feed Ban** – A validated PCR method to detect bovine material has been transferred to ORA. This method is easier to perform than feed microscopy, and the method will increase the number of samples that can be analyzed to help protect the U.S. from possible emergence of BSE.

Dr. McClellan asked if there were new, emerging issues for CVM that were relevant to OR's research programs. Dr. Youngman replied that "the safety of food products from genetically-altered animals is a critical, emerging issue for CVM, and OR scientists are receiving training in this area."

Photo by Kamren A. Kandra

Dr. Larry Kessler, Dr. Mark McClellan and Dr. John Karanian participated in a surgical procedure during the Commissioner's visit to CVM and CDRH's research facility.

International Activities

CVM Official Participates in Risk Assessment Workshop in The Netherlands

Dr. Linda Tollefson, Deputy Director, CVM, was in Noordwijkerhout, The Netherlands, on September 1-5, 2003, as an invited participant in the European Workshop on the Interface Between Risk Assessment and Risk Management.

The Central Science Laboratory of the UK was the lead organizer of this meeting, at the request of the European Commission Quality of Life Programme, Key Action 1 on Food, Nutrition and Health. The purpose was to identify obstacles to the appropriate interaction of risk assessment and risk management in decision-making in the European Union and to recommend ways of improving the interface between risk assessment and risk management, including novel scientific approaches and the research required to develop them. This Workshop is one of several European Commission sponsored activities known as "strategic accompanying measures", which are intended to support the implementation of relevant policy orientations.

□

CVM Scientists Participate in Workshops in El Salvador

Four CVM scientists traveled to San Salvador, El Salvador, from July 21 to 23, 2003, and to Buenos Aires, Argentina from August 7 to 19 to participate in workshops entitled *Enhancing the Participation and Effectiveness of Latin American Countries in the Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF).* The workshops were partially sponsored by the U.S. Codex Office.

The CVM team of scientists represented expertise in both human food safety and veterinary drugs residue control and presented, coordinated, and ran the workshops. Dr. Richard Ellis is a Senior Regulatory Scientist in the Division of Human Food Safety of CVM and he has presented residue chemistry lectures for the World Health Organization/Food and Agriculture Organization (FAO/WHO) Joint Expert Committee on Food Additives (JECFA). Dr. Ellis facilitated the workgroup activities at the workshops and was the principal initiator who organized the workshops in collaboration with the U.S. Codex Office.

Dr. Ana Fernández is a senior toxicologist/microbiologist of the Division of Human Food Safety of CVM, and she has served as an Expert Advisor on the Food Safety Working Group for Veterinary International Conference on Harmonization (VICH) for toxicology assessments. Dr. Fernández has more than 10 years experience in developing human food safety programs in Latin America. Dr. Fernández was co-organizer of the workshops and presented lectures on JECFA and CVM toxicology assessment procedures. Dr. Fernández also acted as an interpreter and facilitator for the workgroup activities.

Dr. Louis Mulligan is the Supervisory Team Leader of Toxicology for the Division of Human Food Safety of CVM. Dr. Mulligan has served as Chairman of the VICH Safety Working Group for international toxicology assessment procedures, and he has participated as a toxicology expert for JECFA and has more than 38 years experience in regulatory toxicology studies with research laboratories and FDA. At the workshop, Dr. Mulligan also lectured on VICH toxicology assessment and JECFA toxicology assessment procedures.

Dr. Lynn Friedlander is the Team Leader of the Residue Chemistry Team of the Division of Human Food Safety of CVM with extensive experience in pharmacology and metabolism. Dr. Friedlander has been a member of the CCRVDF U.S. Delegation and a JECFA participant. She lectured on JECFA food safety procedures with particular expertise in residue chemistry for the workshops.

With a combined number of approximately 100, the attendees included representatives from regulatory authorities responsible for food safety and food export in their countries. The workshops were of significant importance to the Central American and Southern Cone regions of Latin America, and were designed to provide additional understanding of the scientific principles underlying the work of JECFA, the Codex Alimentarius, and the regulatory processes for food safety in the United States.

The workshops also gave CVM a unique opportunity to build improved relationships between its Central American and South American trading partners and to further the networking and communication on issues of mutual concern that arise from CVM's work in the Codex Alimentarius, the WHO, and the FAO, including the JECFA and CCRVDF. □

International Activities *(Continued)*

European Veterinarians Visit CVM

A group of governmental officials responsible for the regulation of veterinary products in several Eastern European countries visited CVM on September 4, 2003. The visitors were part of a U.S. Department of Agriculture-sponsored program called the Cochran Fellowship Program that provides funding for training of agriculturists from middle income and newly emerging countries who are involved in agricultural trade, agribusiness development, and related policy and management.


Photo by Karen A. Kandra

European Veterinarians participating in Cochran Fellowship Program visit CVM.

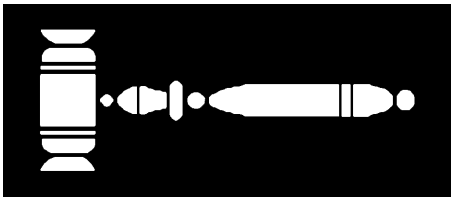
Dr. Mike McWhorter, the USDA's International Training Coordinator from Texas A & M University, explained that "this two-week training program is designed to be an informative and rewarding experience for our international cohorts." Approximately 25 veterinarians participated from Eastern European countries, as well as Ukraine, Russia, Kazakhstan, and Slovak Republic.

Other stops for the group included visiting the APHIS National Center for Import and Export/Regionalizaiton and Evaulation Services at Riverdale, Maryland, a visit to APHIS' Animal Disease Diagnostic Center at Plum Island, New York, and attending a scientific workshop on BSE at Fort Collins, Colorado.

CVM Director, Dr. Steve Sundlof, opened the four-hour CVM visit by welcoming the visitors, and giving a brief overview of CVM activities. CVM officials presented a number of topics, including an overview of the New Animal Drug Process, Drug Residue Safety Evaluation Activities, Pharmacovigilance Responsibilities, Transgenic Animals/Biotech Feeds Activities, Antimicrobial Resistance, and a summary of CVM's International Activities.

Regulatory Activities

by Karen A. Kandra



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

- Garret W. Bootsma Jr., Partner G & J Dairy, Newberry Springs, CA
- Ronnie R. Stewart, Apple Valley, MN
- Clark J. Hiebett, Owner, Rolling Acres Farm, Louisville, GA
- Pete J. VanderPoel, Owner, Sierra Vista Dairy, Tulare, CA
- Brian S. Wind, Partner, T & W Dairy, Bakersfield, CA
- Frank P. & Liduina Barcellos, Partners, Frank and Liduina Barcellos Dairy, Tipton, CA
- Steven L. Carlson, D.V.M., Tipton, CA
- Samuel J. Knevelbaard, Owner, Bayou Vista Dairy, Tipton, CA
- Daniel D. Siemers, President, Siemers Holsteins, Inc., Newton, WI
- Hadwen A. Kieiss, President, Stardell Farms, Inc., Fredericksburg, IA
- David H. Ohman, D.V.M., Glenbeulah, WI

The above violations involved illegal residues of penicillin, flunixin, sulfadimethoxine, tilmicosin in dairy cows.

FDA Strategic Plan Announced

On August 20, 2003, FDA Commissioner Dr. Mark McClellan announced FDA's new Strategic Action Plan, calling it "an aggressive and dynamic plan, requiring hard work and dedication." He added, "It's a plan that we expect to execute within our current resources and budget proposals."

There are five core goals described in the Action Plan. Each goal cuts across most if not all of FDA's Centers, as well as the Commissioner's office. The five goals are:

1 – EFFICIENT, SCIENCE-BASED RISK MANAGEMENT

2 – PATIENT AND CONSUMER SAFETY

3 – BETTER INFORMED CONSUMERS

4 – COUNTERTERRORISM

5 – A STRONG FDA

CVM's Director, Dr. Steve Sundlof said the five goals "track very closely with CVM's Back to Basics initiative." He explained, "One key element of the Agency strategic plan is the use of efficient risk management in our policies and regulations to bring predictability to the drug development process. CVM is firmly committed to this goal, both in the drug review process and in the enforcement and compliance arenas. CVM is developing regulations and guidance to facilitate the review of new biotechnology products, to define the animal drug review process, and to apply risk management to the use of antimicrobial drugs. We are using risk analysis to establish our inspection and enforcement priorities and to frame our guidance on manufacturing practices. Risk analysis is an integral part of our regulatory decision making."

CVM's Back to Basics approach recognizes the importance of establishing

(Continued, next page)

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****.*

I would like to find out where I can get access to what human drugs can be given to dogs and how many milligrams per kilogram for dosing.

Please be advised that human drugs should NEVER be given to pets except under the direction of a veterinarian. While many human drugs are used in companion animal medicine, many of the drugs that humans take can be extremely toxic to our pets (one example is Tylenol, which can be fatal to cats).

Animals may metabolize these drugs differently than humans so it is imperative you consult with your veterinarian.

Are there any drugs/medication that can be given to a dog to halt or reduce their urge to bark?

CVM does not practice veterinary medicine or answer questions related to individual pet care. Your veterinarian is your best source of information for any treatments for your pet. There are medications available that are used in combination with behavior modification to treat separation anxiety in dogs. Your veterinarian can provide information on these treatments.

I am trying to find the correct department to get forms enabling us to keep drugs on site at a new city animal shelter that is currently under construction.

FDA does not register animal care facilities for drug distribution purposes. I suggest you contact your State Board of Pharmacy. If controlled substances are involved, you will also need to contact the Drug Enforcement Administration (DEA)(www.DEA.gov).

If I manufactured ear drops for dogs do they need to have FDA approval?

The Federal Food, Drug, and Cosmetic Act defines drugs as any articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and articles (other than food) intended to affect the structure or any function of the body of man or other animals.

If the ear drops you manufacture are intended for any of these uses, they would need to be the subject of an approved new animal drug application. For information about the new animal drug approval process see *http://www.fda.gov/cvm/index/other/nadaappr.htm*.

Can I import dog food from the UK to the USA for my own private use or would I require some kind of import license?

You can find information about importing animal feed on our web site at *http://www.fda.gov/cvm/index/animalfeed/import_export.htm*, and at *http://www.fda.gov/ora/import/ora_import_system.html*. Please be advised that you will not be able to import foods that contain bovine tissue (beef or dairy cattle) from the UK into the U.S. because there is an import alert on these products because of the presence of bovine spongiform encephalopathy in the UK. The Pet Food Institute (*http://www.petfoodinstitute.org/*), may be able to put you in touch with a manufacturer in the U.S. that uses a similar formulation to what your dogs are accustomed to.

Environmental Warning Added to Animal Euthanasia Products

CVM has approved two supplemental new animal drug applications (NADAs) adding an environmental warning to pentobarbital-containing euthanasia solutions. CVM initiated this label revision in response to reports of wildlife dying as a result of barbiturate intoxication. For example, an article in the Journal of the American Veterinary Medical Association (JAVMA) reported that two bald eagles that fed on the carcass of a euthanized dairy calf were unintentionally poisoned. From 1986 to 2001, the National Wildlife Health Center linked the deaths of 34 eagles to secondary pentobarbital poisoning. Many of these were associated with landfills, involving pets and domestic animals that had been euthanized and had not been covered following disposal in a landfill. To help prevent or alleviate future injury to wildlife, under this supplemental NADA, CVM is requiring that manufacturers revise labels of pentobarbital-containing euthanasia solutions to include a warning statement about the products' hazard to wildlife.

The new, boxed warning will say:

ENVIRONMENTAL HAZARD: This product is toxic to wildlife. Birds and mammals feeding on treated animals may be killed. Euthanized animals must be properly disposed of by deep burial, incineration, or other method in compliance with state and local laws, to prevent consumption of carcass material by scavenging wildlife.

Additional information about this supplemental NADA may be found in the July 21, 2003, *Federal Register* and from Dr. Thomas Moskal at 301-827-2722, e-mail *Thomas.Moskal@fda.gov*.

CVM maintains a program that, in part, consists of a database of adverse drug experiences. Manufacturers of veterinary drugs are required by Federal regulations to report to CVM information concerning any unexpected side effects, injury, toxicity, or sensitivity reaction to their products. CVM uses this information to improve the safety and efficacy of veterinary drugs, such as determining if changes should be made in the product labeling based upon experience with a drug by the general population.

CVM can only include incidents that are reported; and manufacturers only relay those incidents that are reported to them. CVM encourages veterinarians, pet owners, and animal producers to report veterinary adverse events to the manufacturer and to the Center so that they can be included in this database. CVM is particularly interested in receiving information about cases of wildlife intoxication from wildlife veterinarians. The telephone number for reporting adverse drug experiences to CVM is 1-800-FDA-VETS (1-888-332-8387).

FDA Strategic Plan . . . *(Continued)*

strategies and processes for educating stakeholders on how CVM makes critical decisions. The second and third goals of the new FDA Action Plan are to improve patient and consumer healthcare through better information. CVM is working with veterinarians and professional associations to improve communication about drug use and risks.

CVM is also fully engaged in the Agency's efforts to counter terrorism and assure the security of the food supply. CVM scientists are focusing efforts on detecting chemical and biological contaminants in animal feeds in CVM's state-of-the-art research facilities.

[Dr. Steve Sundlof] said "One key element of the Agency strategic plan is the use of efficient risk management in our policies and regulations to bring predictability to the drug development process."

You may read the FDA Strategic Action Plan on the FDA web site at *http://www.fda.gov/oc/mcclellan/strategic.html*.

Comings and Goings

New Hires

Office of New Animal Drug Evaluation (ONADE)

- Dr. Ruth A. Barratt, Veterinary Medical Officer

Departures

Office of the Center Director (OCD)

- Dr. Claire Lathers, Senior Science Advisor

Office of Management (OM)

- Paula Searle, Training Specialist

Office of New Animal Drug Evaluation (ONADE)

- Dr. Kyung Lee, Mathematical Statistician

Retirements

Office of Surveillance and Compliance (OS&C)

- Dorothy Pocurull, Consumer Safety Officer

CVM's Bioengineered Feed Regulatory Program

by W. D. Price, Ph.D.

FDA has the responsibility under the Federal Food, Drug, and Cosmetic Act (the Act), to ensure the safety of all domestic and imported foods intended for human or animal consumption.

CVM partners with the Center for Food Safety and Applied Nutrition (CFSAN) in the FDA regulatory program for foods derived from new plant varieties that includes those developed using the tools of modern biotechnology. These products are also known as genetically engineered or bioengineered foods. Within FDA, CFSAN oversees bioengineered plant products or ingredients intended for human consumption, while CVM plays a similar role when these plant products are used as or in animal feed. Bioengineered foods and food ingredients must adhere to the same standards of safety under the Act that apply to their conventionally bred counterparts. This means that these products must be as safe as traditional foods in the market. FDA has broad authority to initiate regulatory action if a product fails to meet the requirements of the Act.

The United States Department of Agriculture (USDA) and the Environmental Protection Agency (EPA) also regulate new plant varieties. When a bioengineered plant contains a pesticide, it is regulated by EPA, which reviews the safety of the pesticide substance. When necessary, EPA establishes tolerances for pesticidal residues in food or exempts a pesticide from the requirement for a tolerance. FDA enforces these pesticide tolerances in food products. USDA's Animal and Plant Health Inspection Service (APHIS) oversees the agricultural and environmental safety of bioengineered plants during planting and field testing.

CVM and CFSAN have established a consultative process to help developers of new plant varieties comply with the Act's requirements for new foods, including those obtained using biotechnology. Companies have used the consultative process more than 50 times as they sought to introduce genetically altered plants representing 10 different crops into the U.S. market. FDA is not aware of any bioengineered food product on the market under FDA's jurisdiction that has not been evaluated by FDA through the consultation process.

CVM and CFSAN have established a consultative process to help developers of new plant varieties comply with the Act's requirements for new foods, including those obtained using biotechnology.

Typically, a consultation begins early in the product development cycle, before a new variety is ready for marketing. Company scientists and other officials meet with FDA scientists to describe the product under development and often present an anticipated research program. CVM and CFSAN may offer advice on what analyses are appropriate to assess the safety of the bioengineered food.

After the studies are completed, the data and information on the safety and nutritional assessment of the new variety are provided to FDA for review. FDA evaluates the information for all of the known hazards and also for potential unintended effects on plant composition and nutritional properties, since the varieties may contain changes other than those intended by the firm. Specifically, FDA scientists evaluate whether the newly expressed compounds are safe for food consumption, there are no allergens new to the food, no increases in natural toxicants levels, and no reduction of important nutrient levels. They also determine if the food has been changed in any substantive way such that it would need to be special labeling to reveal the nature of the change to consumers.

Some examples of the information reviewed by FDA include: The name of the food and the crop from which it is derived; the uses of the food, in both human food and animal feed; the sources, identities, and functions of introduced genetic material and its stability in the plant; the purpose or intended technical effect of the modification and its expected effect on the composition or characteristic properties of the food or feed; the identity and function of any new products encoded by the introduced genetic material, including estimates of concentration; comparison of the composition or characteristics of the bioengineered food to that of food derived from the parental variety or other commonly consumed varieties with special emphasis on important nutrients, anti-nutrients, and toxicants that occur naturally in the food; information on whether the genetic modification altered the potential for the bioengineered food to induce allergic responses; and, other information relevant to the safety and nutritional assessment of the bioengineered food.

If questions arise about the data provided for a variety, the company may provide a more detailed explanation of a particular issue or may conduct additional studies. FDA's experience has been that no bioengineered product has gone on the market until issues have been resolved.

FDA proposed on January 18, 2001, to replace the voluntary premarket notification program with a mandatory process. More than 100,000 comments were received, and FDA is evaluating

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CVM's Bioengineered Feed Regulatory Program *(Continued)*

the comments. FDA also published on January 17, 2001, a draft guidance document for food manufacturers who wish voluntarily to label their products as to whether they contain bioengineered ingredients or not. The guidance applies to both human food and animal feed. In making these changes, FDA hopes to enhance public confidence in the way in which bioengineered foods are regulated.

FDA also is augmenting its food and veterinary medicine advisory committees by adding scientists with agricultural biotechnology expertise. FDA will use these committees to address over-arching scientific questions pertaining to bioengineered foods and animal feed.

FDA is actively participating in the international harmonization work such as the Codex Committees on food labeling, and the "Ad Hoc Committee on Foods Derived from Biotechnology." The latter committee is especially important because its initial focus is to develop principles and guidelines for the evaluation of the safety of bioengineered foods. CFSAN and CVM are also providing leadership in the Organization for Economic and Cooperative Development (OECD) Task Force on Food and Feed Safety. This Task Force is developing Consensus Papers for use by international bodies regulating bioengineered food and feed.

For more information on CVM consultation process for bioengineered feeds derived from plants, contact W. D. Price, Ph.D. at HFV-220, 7500 Standish Place, Rockville, MD 20855, Telephone 301-827-6652. Email *Bill.Price@fda.gov*, or visit the web sites: *www.fda.gov/cvm* and *www.fda.gov/cfsan*.

Dr. Price is a Special Assistant in CVM's Division of Animal Feeds.

Ruminant Feed (BSE) Enforcement Activities

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

This is an update on FDA enforcement activities regarding the ruminant feed (BSE) regulation. FDA previously provided information on this issue in four CVM UPDATEs, most recently one on April 15, 2002 (*http://www.fda.gov/cvm/index/updates/bseap02.htm*). Since then, FDA has recorded this inspection information in a newly designed database. Throughout the past year, FDA has directed its efforts towards improving the quality of the data available for this report. A new search module for this database is expected to be available in October on the FDA/Center for Veterinary Medicine (CVM) Home Page (*http://www.fda.gov/cvm/index/bse/bsetoc.html*). NOTE: there may be a difference between the numbers in this CVM UPDATE and what one might obtain by querying the posted BSE data. For this CVM UPDATE, FDA's CVM has assembled data from the inspections that have been conducted AND whose final inspection report has been recorded in the FDA's inspection database as of **September 23, 2003.** As of September 23, 2003, FDA had received over 25,000 inspection reports. The majority of these inspections (around 71%) 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 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 were 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 were found that do not meet the threshold of regulatory significance, but do warrant advisory actions to inform the establishment of findings that should be voluntarily corrected. Inspections classified with VAI violations are more technical violations of the Ruminant Feed Ban provisions such as minor recordkeeping lapses and conditions involving non-ruminant feeds.

A NAI inspection classification occurs when no objectionable conditions or

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Ruminant Feed (BSE) Enforcement Activities *(Continued)*

practices were 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". NOTE – A single firm can operate as more than one firm type. As a result, the categories of the different industry segments are not mutually exclusive.

Renderers

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

- **Number of active firms whose initial inspection has been reported to FDA** – 234
- **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.
  - 7 firms (4.5%) were classified as VAI.

Liscensed 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 21 CFR 589.2000.

- **Number of active firms whose initial inspection has been reported to FDA** – 1,110
- **Number of active firms handling materials prohibited from use in ruminant feed** – 300 (27% of those active firms inspected.)
- **Of the 300 active firms handling prohibited materials, their most recent inspection revealed that:**
  - 2 firms (0.7%) were classified as OAI.
  - 15 firms (5.0%) 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** – 5,084
- **Number of active firms handling materials prohibited from use in ruminant feed** – 579 (11% of those active firms inspected.)
- **Of the 579 active firms handling prohibited materials, their most recent inspection revealed that:**
  - 2 firms (0.3%) were classified as OAI.
  - 98 firms (17%) were classified as VAI.

Protein Blenders

These firms blend rendered animal protein for the purpose of producing a quality feed ingredients that will be used by feed mills.

- **Number of active firms whose initial inspection has been reported to FDA** – 220
- **Number of active firms handling materials prohibited from use in ruminant feed** – 62 (28% of those active firms inspected.)
- **Of the 62 active firms handling prohibited materials, their most recent inspection revealed that:**
  - 0 firms (0%) were classified as OAI.
  - 4 firms (6.5%) 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** – 6,905
- **Number of active firms handling materials prohibited from use in ruminant feed** – 1,053 (15% of those active firms inspected)
- **Of the 1,053 active firms handling prohibited materials, their most recent inspection revealed that:**
  - 3 firms (0.3%) were classified as OAI.
  - 137 firms (13%) were classified as VAI.

Total Firms

Note that 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** – 11,375
- **Number of active firms handling materials prohibited from use in ruminant feed** – 1,664 (15% of those active firms inspected)
- **Of the 1,664 active firms handling prohibited materials, their most recent inspection revealed that:**
  - 6 firms (0.4%) were classified as OAI.
  - 171 firms (10%) were classified as VAI.

New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Merial, Ltd. (NADA 141-214)	Ivermectin/Praziquantel (Zimecterin® Gold)	Horses. For control of various internal parasites.	**ORAL**—The NADA provides for use of an ivermectin and praziquantel oral paste. *Federal Register* 06/30/03
Boehringer Ingelheim Vetmedica, Inc. (NADA 141-213)	Meloxicam (Metacam®) RX	Dogs. For the control of pain and inflammation.	**ORAL**—The NADA provides for use of meloxicam oral suspension for the control of pain and inflammation associated with osteoarthritis in dogs. *Federal Register* 07/21/03
Pennfield Oil Co. (NADA 138-934)	Chlortetracycline, Procaine, Penicillin, Sulfamethazine (Pennchlor SP 250), (Pennchlor SP 500)	Swine. For growth promotion, increased feed efficiency, and the management of several bacterial diseases.	**MEDICATED FEED**—The NADA provides for the use of three-way, fixed combination Type A medicated articles containing chlortetracycline, procaine penicillin, and sulfamethazine to make three-way combination drug Type C medicated swine feeds. *Federal Register* 08/08/03
PR Pharmaceuticals, Inc. (NADA 141-040)	Estradiol Benzoate (Celerin)	Steers and heifers. For increased rate of weight gain and improved feed efficiency.	**SUBCUTANEOUS**—The NADA provides for subcutaneous injection, in the ear only, of a suspension implant of estradiol benzoate microspheres. *Federal Register* 08/19/03
PR Pharmaceuticals, Inc. (NADA 141-041)	Estradiol Benzoate (Celerin C)	Suckling beef calves. For increased rate of weight gain.	**SUBCUTANEOUS**—The NADA provides for use of Celerin C, also microspheres for constitution, by subcutaneous injection, in the ear only, for increased rate of weight gain in suckling beef calves. *Federal Register* 08/19/03z

Supplemental New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Alpharma, Inc. (NADA 141-025)	Laidlomycin (Cattlyst®)	Cattle.	**MEDICATED FEED**—The supplement provides for use of CATTLYST Type A medicated articles used to formulate Type C medicated feeds for cattle and for the establishment of a tolerance at 0.2 parts per million for residues of laidlomycin in cattle livers. The previously established ADI for total residues of laidlomycin is also codified at 7.5 micrograms per kilogram of body weight per day. *Federal Register* 07/18/03

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Supplemental New Animal Drug Approvals *(Continued)*

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Schering-Plough Animal Health Corp. (NADA 119-807)	Euthanasia Solution (Beuthanasia-D-Special) RX	Dogs. For humane, painless, and rapid euthanasia.	**SUBCUTANEOUS OR INTRAMUSCULAR**—The supplemental application provides for the addition of environmental warning statements to product labeling. *Federal Register* 07/21/03
Merial, Ltd. (NADA 134-314)	Ivermectin paste (Eqvalan® Paste 1.87%)	Horses. For treatment and control of internal parasites.	**ORAL**—The supplemental NADA provides for the addition of several new species of internal parasites to product labeling for ivermectin paste for horses. *Federal Register* 07/22/03
Pfizer, Inc. (NADA 141-199)	Carprofen (Rimadyl®)	Dogs. For the control of postoperative pain.	**SUBCUTANEOUS**—The supplemental NADA provides for use of carprofen solution in dogs, by subcutaneous injection, for the control of postoperative pain associated with soft tissue and orthopedic surgeries. *Federal Register* 08/18/03

Abbreviated New Animal Drug Approvals

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
West-Ward Pharmaceutical Corp. (ANADA 200-323)	Phenylbutazone RX	Horses. For relief of inflammatory conditions associated with the musculoskeletal system.	**ORAL**—The ANADA provides for oral use of phenylbutazone tablets in horses. West-Ward's tablets are a generic copy of Boehringer Ingelheim Vetmedica's BIZOLIN approved under NADA 99-618. *Federal Register* 07/10/03
Pennfield Oil Co. (ANADA 200-355)	Salinomycin, Chlortetracycline, Roxarsone	Broiler Chickens.	**MEDICATED FEED**—The ANADA provides for the use of single-ingredient Type A medicated articles containing salinomycin, chlortetracycline, and roxarsone to make three-way combination drug Type C medicated feeds. Pennfield Oil Co.'s ANADA 200-355 is a generic copy of Alpharma, Inc.'s NADA 140-867. *Federal Register* 07/10/03

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Abbreviated New Animal Drug Approvals *(Continued)*

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Phoenix Scientific, Inc. (ANADA 200-287)	Gentamicin Sulfate, Betamethasone valerate, Clotrimazole (GBC ointment™) RX	Dogs. For the treatment of otitis externa.	**OPTHALMIC AND TOPICAL**—The ANADA provides for use of gentamicin sulfate, betamethasone valerate, and clotrimazole ointment for the treatment of canine otitis externa associated with yeast and/or bacteria susceptible to gentamicin. GBC ointment is a generic copy of Schering-Plough Animal Health's Otomax approved under NADA 140-896. *Federal Register* 07/21/03
Bioniche Animal Health USA, Inc. (ANADA 200-266)	Phenylbutazone (Butequine) RX	Horses. For relief of inflammatory conditions.	**ORAL**—The ANADA provides for the oral use of Butequine paste in horses for the relief of inflammatory conditions associated with the musculoskeletal system. Butequine is a generic copy of Schering-Plough Animal Health's Phenylzone Paste approved under NADA 116-087. *Federal Register* 07/25/03

Supplemental Abbreviated New Animal Drug Approvals

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Ivy Laboratories Division of Ivy Animal Health, Inc. (ANADA 200-346)	Trenbolone Acetate, Estradiol (Component® TE-H)	Feedlot heifers. For increased rate of weight gain and improved feed efficiency.	**SUBCUTANEOUS**—The supplement provides for the addition of tylosin tartrate to an approved subcutaneous implant containing trenbolone and estradiol. *Federal Register* 07/17/03
Cross Vetpharm Group Ltd. (ANADA 200-144)	Oxytetracycline Hydrochloride (Tetroxy®)	Swine.	**ORAL**—The supplement provides for a new pouch size of oxytetracycline hydrochloride soluble powder used to make medicated drinking water for swine. *Federal Register* 07/21/03
Delmarva Laboratories, Inc. (ANADA 200-071)	Pentobarbital Sodium and Phenytoin Sodium (Euthasol™) RX	Dogs and others. For humane, painless, and rapid euthanasia.	**SUBCUTANEOUS OR INTRAMUSCULAR**—The supplement adds an environmental warning statement to product labeling. *Federal Register* 07/21/03
Ivy Laboratories Division of Ivy Animal Health, Inc. (ANADA 200-346)	Trenbolone, Estradiol (Component® TE-200)	Feedlot steers. For increased rate of weight gain and improved feed efficiency.	**SUBCUTANEOUS**—The supplemental ANADA provides for an additional dose of trembolone acetate and estradiol implant. *Federal Register* 08/15/03

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HEALTH & HUMAN SERVICES

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03-7433