FDA VETERINARIAN
Center for Veterinary Medicine
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Draft Compliance Policy Guide Explains Voluntary Self Inspection of Medicated Feed Manufacturing Facilities

The Food and Drug Administration has announced a draft Compliance Policy Guide (CPG) to provide guidance to FDA field offices to help prioritize inspections of medicated feed manufacturing facilities based on a number of factors, including whether the facility conducts self-inspections. The draft CPG describes a proposed approach for medicated feed manufacturing facilities to conduct self-inspections to determine compliance with the Federal Food, Drug, and Cosmetic Act (FFDCA) and the appropriate regulations (21 Code of Federal Regulations, Part 225) with respect to the manufacture and distribution of medicated animal feed (i.e., animal feed containing approved new animal drugs). In addition to seeking comments on this new concept, FDA is considering piloting the new voluntary self inspection approach for at least one year. The pilot would be announced in a future *Federal Register* notice.

Manufacturers of medicated animal feeds

Medicated feed is usually manufactured at commercial establishments and on-farm mixer/feeder operations which are made up of both licensed and unlicensed facilities. FDA conducts inspections of licensed and unlicensed feed mills. There are approximately 1,130 FDA-licensed feed mills and 5,500 non-FDA-licensed commercial feed mills in the United States; the number of non-FDA-licensed on-farm mixer/feeder operations is not known. Many of the feeds being manufactured at these facilities are designed for use in food-producing animals, thereby necessitating oversight to ensure that any edible products from animals that consume these feeds are safe and do not contain potentially hazardous residues of drugs. Also, medicated animal feed needs to be produced properly in order to protect the health and safety of the animal itself.

(Continued, next page)

Pet Food Recall

Since mid-March, the Food and Drug Administration has been working diligently to investigate the contamination of certain pet food ingredients with melamine and melamine-related compounds and to contain the distribution of the contaminated products.

Immediately after FDA received the initial reports about the problem, it began an extensive program of recall coordination, inspections, and product tracking. FDA's Office of the Commissioner, the Center for Veterinary Medicine, and the Office of Regulatory Affairs have been leading the effort. Within the Federal Government, FDA has consulted with the Centers for Disease Control and Prevention and the U.S. Department of Agriculture. Outside government, FDA has been working with universities, Banfield Pet Hospitals (a network of pet hospitals across the country), the Veterinary Information Network, the American Association of Veterinary Laboratory Diagnosticians, and other groups.

FDA has also taken extra steps to keep consumers informed and to be a source of up-to-date, reliable information. FDA continues to place as much information as possible on the FDA Web site, including a searchable database of all pet foods subject to the recall, so consumers can quickly determine what pet food is safe to use.

When the investigation is complete, *FDA Veterinarian* will present a full report of the recall.

In the meantime, interested stakeholders should continue to go to the FDA Web site for the latest information. (*http://www.fda.gov/oc/opacom/hottopics/petfood.html*)

In This Issue

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

Draft Compliance Policy Guide... *(Continued)*

Medicated feeds must comply with manufacturing controls specified in the current Good Manufacturing Practice for Medicated Feeds regulations (cGMP). The cGMP regulations (21 CFR 225) represent minimum standards that producers of medicated feed must adhere to, or else be subject to adulteration sanctions set forth in Section 501(a)(2)(B) of the FFDCA. These minimum standards help ensure that the drugs (including drugs contained in animal feeds) produced meet the requirements of the FFDCA as to safety and that they have the identity and strength, and meet the quality and purity characteristics that they claim to have.

Section 510(h) of the FFDCA requires inspection of every FDA-licensed feed mill at registration and at least once in every 2-year period after that. Non-FDA-licensed feed mills are also subject to inspection. However, there is no requirement that such facilities be inspected every 2 years.

Routine self-checking for compliance with cGMP by feed manufacturing operations is not a consistent practice in the industry; some do and some do not. Among the ones that do, some have quality assurance programs that include some kind of periodic audit or assessment procedure of "self inspection." This concept of "self inspection" was incorporated in a proposed Model National Medicated Feed Program sponsored by the Association of American Feed Control Officials. As noted in the draft CPG, FDA encourages the use of quality assurance programs that include internal audits or assessments for compliance with cGMP.

Inspection priorities

As part of the agency's determination of priorities for cGMP inspections of medicated feed manufacturing firms, it intends to consider whether the establishments follow the approach outlined in the section of the CPG entitled, "Voluntary Self Inspection Conduct and Reporting." A higher priority for inspections will be given to those medicated feed manufacturers that do not correct cGMP violations after an opportunity for correction and/or those that do not conduct self inspections as outlined in the CPG. By doing this, FDA will be able to focus more effectively its available resources on monitoring and inspecting medicated feed manufacturers that have a history of non-compliance with cGMP or about which the agency has no information about their compliance. It will also allow FDA to recognize the proactive and successful efforts of those feed manufacturing establishments that have taken steps to ensure cGMP compliance. The various steps to follow and a description of the forms to be used for voluntary self inspection conduct and reporting are detailed in the CPG. However, as noted in the CPG, nothing contained in the draft document restricts FDA from conducting inspections or affects the legal responsibilities of medicated feed establishments.

Paperwork estimates

The agency expects approximately 1,000 feed mills will conduct self inspections; 800 of these are expected to be licensed and 200 are expected to be non-licensed. FDA also expects that 9 hours will be needed for each licensed facility to review any previous self inspection, conduct an inspection, and complete the report; non-licensed facilities are expected to need only 4 hours each. The agency also expects that completing and sending the voluntary self inspection notifications to FDA will take 15 minutes per firm.

For questions

The notice of availability published on February 12, 2007 (72 F.R. 6572) (*http://www.fda.gov/OHRMS/DOCKETS/98fr/E7-2232.pdf*), and the comment period on the draft guidance document closed April 30, 2007. However, in a *Federal Register* notice that published on May 4, 2007, the comment period was reopened for 30 days to allow comments through June 4, 2007. The actual draft guidance document is available electronically at: *http://www.fda.gov/OHRMS/DOCKETS/98fr/07d-0027-gdl0001.pdf*. Questions regarding the draft CPG may be directed to the CVM contact, Paul Bachman, CVM, HFV-320, FDA, 7519 Standish Place, MPN-4, Room 128, Rockville, MD 20855; ph: 240-276-9225; e-mail: *Paul.Bachman@fda.hhs.gov*.

Clarification

In issue 2006 – No. V, *FDA Veterinarian* reported on two Warning Letters issued because violative penicillin residues found in tissues of animals offered for sale for human food. The *FDA Veterinarian* reports incorrectly implied that a veterinarian must personally administer the drugs used extralabel or be in violation of the animal drug regulations. The regulations do not require that veterinarians personally administer drugs. The regulations require that the drugs used extralabel be administrated under the direction of a licensed veterinarian who is functioning under a valid Veterinarian/Client/Patient Relationship, and that other precautions be taken.

FDA VETERINARIAN

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THREE IMPORTANT APPROVALS UNDER THE MUMS ACT

35% PEROX-AID® Garners Approval for Bacterial Ailments

by Jennifer Matysczak, V.M.D., Aquaculture Drugs Team, Office of New Animal Drug Evaluation

A chemical firm, taking advantage of a key provision of the Minor Use and Minor Species Animal Health Act (MUMS Act), has used data developed through an aquaculture drug public partnership to gain approval of an important drug for finfish.

The company, Eka Chemicals, Inc., Marietta, GA, is the sponsor of the approved aquaculture drug, 35% PEROX-AID®. The drug's active ingredient is hydrogen peroxide.

35% PEROX-AID® was approved for the control of mortality in:

- Freshwater-reared finfish eggs due to saprolegniasis;
- Freshwater-reared salmonids due to bacterial gill disease associated with *Flavobacterium branchiophilum*; and
- Freshwater-reared coolwater finfish and channel catfish due to external columnaris disease associated with *Flavobacterium columnare (Flexibacter columnaris)*.

Bacterial gill disease and external columnaris disease are two significant hatchery diseases, and 35% PEROX-AID® is the first drug approved to treat these diseases.

The product was approved for over-the-counter sale. The approved method of administration for all claims is immersion. The withdrawal time (the time before the fish can be harvested for market or be released into public waters) is zero days.

Eka Chemicals, principally a chemical supplier to the pulp and paper industries, leveraged data generated in the public sector to demonstrate the safety and effectiveness of hydrogen peroxide and demonstrated that it could produce 35% PEROX-AID® under Good Manufacturing Practices.

35% PEROX-AID® is the first new immersion therapeutic drug approved for finfish in 20 years. This approval is also the first original drug approval with multiple claims encompassing a variety of finfish species and life stages.

MUMS designation

35% PEROX-AID® was designated for the three approved claims under the MUMS Act. A sponsor can apply to CVM to have a drug given designation status under the MUMS Act prior to approval or conditional approval. Designation status provides benefits to drug sponsors to encourage them to develop drugs for minor uses and minor species. Sponsors who gain approval for designated new animal drugs will be granted 7 years of exclusive marketing rights, which means the sponsor will face no competition in the marketplace for the approved use of the drug for that time period. Eka Chemicals has marketing exclusivity for each of the three approved claims.

35% PEROX-AID® is the second aquaculture drug approval to benefit from the designation provisions of the MUMS Act. The first was AQUAFLOR® Type A Medicated Article (florfenicol), an antimicrobial for the control of mortality due to enteric septicemia of catfish. Currently, 40 of the 44 drug designations granted by CVM are for claims for aquatic species.

The MUMS Act, patterned after the successful human Orphan Drug Act of 1983, was a response to the lack of economic incentive for drug sponsors to develop drugs for minor species and for minor uses (rare diseases) in major species. The MUMS Act defines "major species" as cattle, horses, swine, chickens, turkeys, dogs, and cats. "Minor species" are species not listed as one of the seven major species. Therefore, under the MUMS Act, fish are minor species.

Data development by the public sector

The Federal-State Aquaculture Drug Approval Partnership Project contributed funds towards hydrogen peroxide research efforts. The partnership involves 38 states, each of which contributed $20,000 per year for 8 years (1994-2002) to aid in the development of drugs needed for aquaculture. Hydrogen peroxide is one of eight project drugs the partnership identified as important. The others are florfenicol, oxytetracycline, isoeugenol, chloramine-T, copper sulfate, potassium permanganate, and formalin. The program has resulted in approvals for a significant number of label claims for four of these products, and work continues.

The Upper Midwest Environmental Sciences Center (UMESC), which is part of the United States Geological Survey, generated effectiveness and target animal safety data necessary for the approval. UMESC, located in La Crosse, WI, also prepared the environmental assessment for the application.

UMESC's work is available in a Public Master File that can be referenced by a drug or chemical company to complete a New Animal Drug Application. For example, the target animal safety data generated by UMESC can be used to support additional claims for the use of hydrogen peroxide on freshwater-reared finfish and eggs.

Environmental considerations

Working with the U.S. Environmental Protection Agency, CVM developed an acute water quality benchmark

(Continued, page 5)

THREE IMPORTANT APPROVALS UNDER THE MUMS ACT *(Cont.)*

Antimicrobial OK'd to Control Coldwater Disease Mortality in Salmonids

The Food and Drug Administration recently approved AQUAFLOR® (florfenicol) Type A medicated article for the control of mortality in freshwater-reared salmonids due to coldwater disease associated with *Flavobacterium psychrophilum*.

AQUAFLOR® is the first drug approved by FDA for use during coldwater disease outbreaks. The drug is an important disease management tool for aquaculture and fisheries programs.

Coldwater disease is an acute septicemic infection occurring primarily in salmonid fish species. *F. psychrophilum*, the causative agent, is considered a serious salmonid pathogen in the United States. The disease causes significant losses of hatchery-reared salmonids, including losses at state and federal hatcheries producing fish for native species restoration programs. Up to 50 percent of affected fish may be lost during disease outbreaks, with greater mortality in younger fish.

FDA approved the product as a Veterinary Feed Directive drug, meaning that the medicated feed can be fed only on the order of a licensed veterinarian. Extralabel use of medicated feed containing florfenicol is prohibited.

AQUAFLOR® for the approved label indication is designated under the Minor Use and Minor Species Act of 2004, which entitles Schering-Plough Animal Health Corporation up to 7 years of exclusive marketing rights beginning on the date of approval.

This approval is the result of cooperation between a pharmaceutical company, Schering-Plough Animal Health Corp., Summit, NJ, and public sector researchers. The Fish and Wildlife Service, Aquatic Animal Drug Approval Partnership Program, Bozeman, MT; U.S. Geologic Survey, Upper Midwest Environmental Sciences Center, La Crosse, WI; and the Montana Department of Fish, Wildlife, and Parks generated data for the approval.

FDA reviewed extensive data to make sure the product met all necessary effectiveness, target animal safety, human food safety, and environmental safety standards. FDA has concluded that freshwater-reared salmonids fed florfenicol are safe for human consumption when florfenicol is administered according to the label directions.

As part of the human food safety requirements, AQUAFLOR® was reviewed under the Center for Veterinary Medicine's Guidance for Industry, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern." The Guidance provides a regulatory pathway sponsors can use to show how an antimicrobial drug can be used in food-producing animals without endangering public health. CVM has determined that antimicrobial resistance risk management strategies (as described in the Guidance) in place for AQUAFLOR® are appropriate for its conditions for use.

First Ever Conditional Approval Under MUMS

The Food and Drug Administration has announced the first ever "conditional approval" of a product, as authorized under the Minor Use and Minor Species Animal Health Act (MUMS Act) of 2004, which allows the sponsor to begin marketing a product while continuing to collect substantial evidence of effectiveness.

The product is AQUAFLOR®-CA1 (florfenicol) Type A medicated article for the control of mortality in catfish due to columnaris disease associated with *Flavobacterium columnare*. Columnaris disease is a major bacterial disease of catfish in the United States, and is estimated to cause up to 25 percent of the disease losses in catfish annually.

As the product name indicates, the "CA" means that the drug is conditionally approved, and the number "1" means that this is the first conditionally approved application for this formulation. In addition, the product labeling includes a specific statement required by the MUMS Act, "Conditionally approved by FDA pending a full demonstration of effectiveness under application number 141-259."

Conditional approval allows the sponsor to market a drug before collecting all necessary effectiveness data as long as the sponsor has demonstrated that there is a reasonable expectation that the drug is effective. The sponsor may continue marketing AQUAFLOR®-CA1 for up to 5 years, subject to annual renewals, while collecting substantial evidence of effectiveness.

The sponsor is Schering-Plough Animal Health Corporation, Summit, NJ. FDA announced the conditional approval in April.

FDA reviewed extensive data to ensure the product met all necessary target

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THREE IMPORTANT APPROVALS UNDER THE MUMS ACT *(Cont.)*

35% PEROX-AID®... *(Continued)*

for hydrogen peroxide. Users of 35% PEROX-AID® should inform the appropriate authority under the National Pollutant Discharge Elimination System (NPDES) of their intent to use the drug. The acute benchmark concentration is not an effluent discharge limit, but the appropriate NPDES authority can use it in conjunction with site-specific information to determine if a specific discharge limit, effluent monitoring, or both, are required at specific aquaculture facilities. For more information regarding the acute water quality benchmark for hydrogen peroxide, go to CVM's Web site at *http://www.fda.gov/cvm/CVM_Updates/perox-aid2.htm*.

New horizon for aquaculture drugs

The approval of 35% PEROX-AID® expands the medicine chest available to those caring for fish. Data development sponsored by the Federal-State Aquaculture Drug Approval Partnership Project and other public entities, in addition to traditional drug development by pharmaceutical sponsors, continues with the goal of approval for more drugs and claims for aquaculture use.

Animal By-Products Renderer Signs Consent Decree

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

A consent decree of permanent injunction has been signed by the Food and Drug Administration and the president and vice president/general manager of Holmes By-Products Co., Inc., of Millersburg, OH, a renderer of bovine and poultry materials. The firm was found to be in violation of FDA's ruminant feed ban (21 CFR Section 589.2000).

The ruminant feed ban, published in 1997, is an important safeguard against the establishment and spread of bovine spongiform encephalopathy (BSE) in the United States.

Holmes By-Products, Inc., and its officers have agreed to incorporate a combination of one or more of the following mitigation steps: label all of its products with the statement "Do not feed to cattle or other ruminants," maintain separate lines of equipment for producing various products, and sufficiently clean existing equipment between uses. Under the terms of the consent decree, FDA retained permission to inspect the facility without prior notice to ensure continued compliance with the consent decree. In addition, the defendants agreed to pay the costs of all FDA inspections, investigations, and analyses that the agency deems necessary to ensure compliance.

The consent decree, which was entered on February 26, 2007, in the U.S. District Court for the Northern District of Ohio, also provides for FDA to require a recall or shutdown of the firm should violations occur in the future. Consecutive inspections of the Holmes operation by FDA officials showed that the company used common equipment to manufacture mammalian meat and bone meal and poultry byproduct meal products without using a clean-out process adequate to avoid and prevent commingling and cross-contamination. Although serious deviations from the ruminant feed ban were found, no evidence was found to indicate that this poultry byproduct meal had actually been fed to cattle or other ruminants.

First Ever Conditional Approval Under Mums *(Continued)*

animal safety, environmental safety, and human food safety standards. FDA concluded that catfish fed florfenicol are safe for human consumption when florfenicol is administered according to the label directions. FDA also concluded that the data submitted demonstrated that there is a reasonable expectation that AQUAFLOR®-CA1 is effective for columnaris disease in catfish.

AQUAFLOR®-CA1 is a veterinary feed directive drug, meaning that the medicated feed can be fed only on the order of a licensed veterinarian. The extralabel or off label use of medicated feed containing florfenicol is prohibited.

AQUAFLOR®-CA1 has been declared a designated new animal drug by FDA under provisions of the MUMS Act. This designation entitles AQUAFLOR®-CA1 to 7 years of exclusive marketing rights beginning on the date of conditional approval. The exclusive marketing rights associated with the designation status protect against generic copying and other pioneer products for the same drug with the same formulation and intended use.

If the drug does not have designation status, even if it is destined for use in a minor species or for a minor use, the regular exclusivity rules apply as for any New Animal Drug Application. The protection is only against generic copying. The sponsor should qualify for 5 years of exclusivity for an original (new entity) application and for 3 years for a supplemental application. The protection for the supplemental application relies on the sponsor having provided significant new data supporting target animal safety or effectiveness to gain the approval.

FDA Approves Drug to Prevent, Treat Vomiting in Dogs

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

On February 28, 2007, the Food and Drug Administration announced the approval of two formulations of a new class of drug that is effective against certain causes of vomiting in dogs.

The tablet form of the new product, CERENIA™ (maropitant citrate), is approved for the prevention of acute vomiting, as well as vomiting due to motion sickness. CERENIA™ Injectable Solution is approved for the prevention and treatment of acute vomiting. Both products, which are made by Pfizer, Inc., are available only by order of a veterinarian.

According to Pfizer Animal Health market research, veterinarians see 30 cases of vomiting due to various causes per month on average, with an estimated 2.8 million dogs experiencing vomiting each year in the United States. Dogs undergoing cancer treatment or suffering from a paroviral infection, kidney disease, pancreatitis, and other ailments can suffer from acute vomiting, which can lead to weakness, dehydration, electrolyte imbalances, and even death.

In addition, another 1.2 million dogs suffer from vomiting caused by motion sickness. Motion sickness can be a major problem for dogs; some can become ill as quickly as 5 minutes after the start of a trip in a vehicle.

In one of the studies supporting the approval of the drug, CERENIA™ Injectable Solution was tested in dogs with cancer undergoing chemotherapeutic treatment with cisplatin, an agent that induces strong vomiting. In these trials, CERENIA™ Injectable Solution was 95 percent effective in preventing vomiting due to cisplatin.

As indicated in the product labeling, CERENIA™ is recommended for use in dogs 16 weeks of age and older. It is administered once a day, in either the tablet or the injectable form, to prevent acute vomiting for up to 5 days. To prevent vomiting due to motion sickness, the tablet(s) is to be given 2 hours prior to travel. Side effects observed during the company's clinical trials using the tablets for the prevention of vomiting due to motion sickness include excessive salivation, vomiting not associated with motion sickness, and muscle tremors. Side effects observed during the company's clinical trials using the tablet and the injectable for the prevention of acute vomiting include diarrhea and anorexia.

CERENIA™ has not been evaluated in dogs used for breeding, pregnant or lactating dogs, dogs with gastrointestinal obstruction, or dogs that have ingested toxins.

According to Pfizer, the new product will be available in the summer of 2007.

CVM Approves Drug to Treat Obesity in Dogs

(Due to a printing error, part of this article, which appeared on page 1 of the previous edition of FDA Veterinarian, was deleted in the previous issue. Here is the complete article.)

The Center for Veterinary Medicine in early January 2007 approved the first-ever drug for the management of obesity in dogs in the United States.

The product is Slentrol™ (dirlotapide), and the sponsor is Pfizer, Inc., New York, NY.

The product will be available only by prescription from a veterinarian.

The drug is given to the dog in varying amounts over the course of the treatment. The dog is given an initial dose for the first 14 days. After that, the veterinarian will assess the dog's progress at monthly intervals, adjusting the dose depending on the dog's weight loss. After the dog has achieved the goal weight, the drug's manufacturer recommends continued use of the drug during a 3-month period, while the veterinarian and dog's owner establish the optimal level of food intake and physical activity needed to maintain the dog's weight.

Slentrol™ is a new chemical entity. It is a selective microsomal triglyceride transfer protein inhibitor that blocks the assembly and release of lipoproteins into the bloodstream. Scientists do not completely understand the drug's mechanism for producing weight loss, but it seems to result from reduced fat absorption and by providing a satiety signal from lipid-filled cells lining the dog's intestine.

Adverse reactions include vomiting, loose stools, diarrhea, lethargy, and loss of appetite.

The product is not for use in humans. It carries the standard warning, "Not for use in humans. Keep this and all drugs out of reach of children." The labeling also cites adverse reactions associated with human use, including abdominal distention, abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting.

Many dogs in the United States are overweight and obese. Veterinarians generally agree that dogs weighing 20 percent more than ideal weight are obese.

Developments in New Animal Technologies Show Rapid Advancement: CVM Keeping Pace

In trying to increase the food production efficiency and health of animals, the livestock and pharmaceutical industries have been looking beyond traditional approaches, such as diet improvements, selective breeding programs, and drug development. Advanced forms of assisted reproductive technologies, new approaches to making and targeting drugs, and novel methods to alter the genetic makeup of animals are being used to unlock secrets into faster growing livestock, tastier and more healthful food products from animals, more environmentally friendly farming, and even the use of animals to produce human drugs and organs. These new technologies are yielding exciting developments into understanding the very being of life.

The Center for Veterinary Medicine in the Food and Drug Administration is keeping up-to-date on these developments to ensure the safety of food and other products as well as the health of animals developed through these technologies.

by Suzanne Sechen, Ph.D., Office of New Animal Drug Evaluation

Cloning

Starting with artificial insemination and followed by embryo transfer, the livestock industry has been using assisted reproductive technologies for decades to acquire better genetics at a faster pace than that offered by traditional selective breeding methods. Cloning is an advanced form of assisted reproductive technology that has captured considerable public attention.

The ability to copy prized livestock and preserve the genetics of threatened species are some of the goals of animal cloning.

Cloning is essentially asexual reproduction, and it produces offspring that are genetically identical to the genetic donor. Early attempts at cloning in the 1970s involved techniques such as splitting an already formed embryo or blastomere nuclear transfer, which fused the nucleus of an embryo cell with an unfertilized egg that has had its own nucleus removed. However, characteristics of the animal clone resulting from these techniques were unpredictable because traits of the embryo could not be known until after the animal was born. The procedures also yielded a limited number of animal clones.

In the mid-1990s, cloning technology took a big step forward with the development of a technique called adult or somatic cell nuclear transfer (SCNT). The first successful SCNT cloning produced the famous Scottish sheep named Dolly. The new technique fuses the nucleus from a differentiated adult animal cell (such as a skin cell or kidney cell) with an unfertilized egg that has had its own nucleus removed. The new nucleus contains all the genetic material needed to create the clone. Biologists then stimulate the newly formed cell to reprogram the donor nucleus to behave as if it has just been fertilized, and initiate embryo development. The embryo is placed into a surrogate dam by a routine embryo transfer technique for gestation and birth. The SCNT approach allows copying of adult animals whose traits are well-known.

CVM carefully reviewed the critical issues of the safety of food products for human consumption from cattle, swine, goat, and sheep clones and their sexually reproduced offspring and the safety of the technology to the animals. The Center released on December 28, 2006, a Draft Animal Cloning Risk Assessment, Proposed Risk Management Plan, and a Draft Guidance for Industry, culminating years of a rigorous and transparent review process.

During this period, CVM continued to ask producers and breeders of clones to not introduce food products (such as milk or meat) from animal clones or their progeny into the human or animal food supply. The Draft Risk Assessment drew from published scientific literature, data from cloning companies, and preliminary evaluations. It concludes that, although there are risks to animals involved in the cloning process, cloning technology does not present any unique risks that have not already been observed in animals produced using other forms of assisted reproduction. However, the adverse outcomes may occur at a higher frequency with cloning than with other assisted reproductive technologies now in common use, such as *in vitro* fertilization or embryo transfer. The Assessment also concludes that food products derived from cattle, swine, and goat clones and any clone offspring are as safe to eat as food from their non-clone counterparts. Healthy adult clones are virtually indistinguishable from their conventional counterparts.

Biotechnology

Biotechnology might simply be defined as the use of biological processes to make or modify products. The term "biotechnology" often implies the use of recombinant DNA. A number of biotechnology processes and products involving or relating to animals are of potential regulatory interest to CVM.

(Continued, next page)

Developments in New Animal Technologies . . . *(Cont.)*

Prior to the development of recombinant DNA technology, drug sponsors could manufacture large protein drugs (e.g., insulin, somatotropin, and prolactin) only by isolation and purification from animal endocrine organs or body fluids. High costs, purification difficulties, and low output made these products prohibitive for use in animal agriculture. The situation changed in the 1980s when recombinant DNA (rDNA) technology allowed drug sponsors to use bacterial fermentation systems of transformed microorganisms as factories to produce large quantities of protein drugs at relatively low cost. The technology involves isolation of a desired gene that codes for the protein of interest and inserting it into a bacterial host, usually *Escherichia coli*. The protein product is isolated and purified from the bacteria.

This approach to producing drugs required new approaches by the FDA to review the manufacturing capabilities of the drug sponsor. However, the drugs themselves are reviewed for safety and effectiveness similar to other new animal drugs developed using more conventional methods. A recombinant bovine somatotropin (rbST) product approved by FDA in 1993 to increase milk production in dairy cows is produced with this technology.

Genetic engineering using rDNA has progressed beyond the modification of bacteria and plants, and has advanced to the point where it is now possible to use the same technology to introduce desired changes into animals. Various techniques are used to produce genetically engineered animals, such as using components of viruses to introduce the rDNA into cells, microinjection of the gene(s) of interest into early embryos, taking advantage of the cell's normal physiology to insert gene(s) of interest into specific regions of the genome, or by genetically modifying somatic cells, followed by their use in SCNT.

It is important to note that genetically engineered animals produced by SCNT are not the subject of the agency's Draft Risk Assessment on Animal Cloning released last December. Animal clones do not have any additional DNA added to them, and they are intended to help propagate naturally occurring, desirable traits throughout the herd.

Objectives of genetic engineering in animals are broad. Added genes might enhance disease resistance, increase size, improve food production efficiency, produce lean meat that remains tender, or animal food products with a fat content considered more healthful for humans. Beyond agricultural interests, scientists are evaluating "biopharm" uses of animals. For example, much like the use of transformed *E. coli* to produce protein drugs, biopharmaceutical substances might be produced inexpensively in the milk or eggs of animals. Scientists are also examining the use of genetically engineered animals to produce tissues (including blood) or organs that will not be rejected by the human body to help meet the growing needs for organ and tissue replacement.

Another potential application of genetic engineering is gene therapy, which introduces genetic material into the body to replace faulty (mutated) or missing genetic material responsible for diseases or other abnormal conditions. The most common approach to gene therapy is to insert a normal gene to replace the abnormal gene in affected (target) cells using a carrier molecule. Modified viruses are typically used as the carrier, although fatty particles called liposomes are also being tested for this purpose. Other gene therapy techniques are also being evaluated, such as inactivating ("knocking out") mutated genes that are not properly functioning, or reverse mutations to repair an abnormal gene. Many technical challenges must be overcome before gene therapy will be a practical approach to treating disease. For example, scientists must find better ways to deliver genes and target them to particular cells. They must also ensure that new genes are precisely controlled by the body.

Biotechnology also affects the feeds given to animals. Bioengineered feeds, such as corn, soybeans, and cotton by-products have been developed by inserting genes that, for example, improve insect resistance and plant tolerance to herbicide application to improve the control of weeds.

Genomics, proteomics, and pharmacogenomics

Also of interest to the FDA and pharmaceutical industry are the related fields of genomics, proteomics, and pharmacogenomics. Although not subject to regulatory approval by FDA in the same way as drugs and genetically engineered animals, these fields serve as tools to study gene expression and drug responsiveness. The information gained from these fields may ultimately play an important role in preventing, diagnosing and treating a variety of diseases. The focus of these fields is how information encoded in an individual's genes is converted into the actual functioning of cells and, ultimately, the body. Genes are made up of DNA, which is "transcribed" into RNA. The cell then "translates" the RNA to synthesize proteins. These proteins and their products are fundamentally responsible for all cellular behavior.

- Genomics is the study of genes and their interactions and function in the whole living organism.
- Proteomics defines the proteins encoded by a specific gene. It identifies when and where proteins are produced in a cell so as to establish their physiological

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Developments in New Animal Technologies . . . *(Cont.)*

roles in an organism. Proteomics also examines how protein synthesis in cells is changed in response to different environments, such as a drug treatment or a disease state.

- Pharmacogenomics studies how the genetic makeup of an organism affects its response to drugs in terms of both safety and effectiveness. Examination of drug responsiveness in specific populations or disease states and how the drug response is altered by genetic variation might allow more specific targets for drug treatments, more precise dose levels, and improved safety.

Nanotechnology

One of the newest areas of interest in pharmaceuticals is nanotechnology. The premise behind this technology is that tiny structures with unique properties and functions due to their size are able to penetrate tissues with little impediment. In terms of pharmaceutical uses, interest lies in designing the particles to target and even repair specific diseased cells. The manufacturing of these products and their safety and effectiveness would be regulated by FDA. Like many of these new technologies, FDA's review of new drugs based on nanomaterials may require new approaches to assessing safety and effectiveness.

Working group

With the rapid development of new technologies involving animals, CVM developed an internal working group, involving scientists representing different areas of expertise. This group, the Animal Biotechnology Working Group (ABWG), keeps abreast of the latest developments in new technologies and keeps the Center and its management apprised of those developments. (See related article, "Working Group Keeps CVM Abreast of New Animal Technologies.")

Working Group Keeps CVM Abreast of New Animal Technologies

by Suzanne Sechen, Ph.D., Office of New Animal Drug Evaluation

The Center for Veterinary Medicine in the Food and Drug Administration recognizes the regulatory challenges presented by new approaches to increase the food production efficiency and health of animals. Clearly, Center scientists need to stay up-to-date on technological processes and concerns to help guide CVM and FDA to make sound regulatory decisions and to communicate these decisions to the public. To this end, in 2001 CVM established the Animal Biotechnology Working Group (ABWG).

The ABWG provides a science-based forum within CVM to promote greater understanding of not just biotechnology-derived products and genetically engineered animals, but also advanced forms of assisted reproductive technology and new approaches to making and targeting drugs. Membership consists of scientific reviewers, researchers, and managers in CVM's Office of New Animal Drug Evaluation, Office of Surveillance and Compliance, and Office of Research interested in new technologies. The wide representation across the Center provides members a broad source of information from all regulatory perspectives and also promotes better communication and consistency on decisions within CVM on new issues.

Members of the ABWG develop expertise in the latest advancements in new technologies, and they attend and participate in scientific meetings to communicate the agency's processes and concerns in regards to these technologies as applied to animals. They provide scientific leadership and technical assistance to CVM and FDA with respect to policy decisions, position papers, guidance documents, and scientific reviews, thereby protecting public, animal, and environmental health.

Emerging technologies

The ABWG serves a critical role in increasing Center awareness and knowledge about emerging technologies and critical regulatory issues related to these technologies.

Members of the ABWG continue their own education in order to best serve the needs of the Center. For example, members attend lectures and hands-on courses at the National Institutes of Health (NIH) for experience with basic recombinant DNA technology, cloning techniques, proteomics, and nanotechnology.

They also learn specific tools, such as polymerase chain reaction (PCR) and microarray technology. PCR is a technique used to amplify the number of copies of a specific region of DNA in order to produce enough DNA to be adequately tested.

Microarrays identify DNA, RNA, or proteins in cells or tissue samples. Microarrays are extremely useful for characterizing early changes that occur as the result of administering a drug or developing a genetically engineered animal. For example, if an animal is

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Working Group Keeps CVM Abreast... *(Continued)*

treated with a new drug that may have effects on liver function, scientists can use microarrays to determine the dose levels associated with very early liver changes to help drug developers find less toxic doses. DNA microarrays include thousands of samples of known DNA sequences (for example, genes known to be associated with detoxifying certain classes of drugs in the liver) fixed in specific locations to a support (e.g., glass slide or nylon membrane) in a "grid" design. A sample of RNA from the liver of a treated animal is tagged with fluorescent dye and then hybridized to the array. Only the RNA sequences that correspond to genes that are being expressed to detoxify that drug will bind to those genes (which have been immobilized on the grid), and fluoresce. This process is visualized as bright green or red "dots." Brighter dots would indicate that more of the RNA was present, and could be used to help understand how the drug exerts its toxic effect.

Members of the ABWG attend scientific conferences to learn about recent research developments in new technologies as well as issues and concerns associated with these developments.

The ABWG also plays a significant role in educating the Center. It has invited experts from FDA, NIH, the U.S. Department of Agriculture (USDA), and various universities to educate CVM scientists on issues such as risks associated with the use of viral sequences as methods for introducing genes of interest into cells or organisms, the potential environmental impact of the release of genetically engineered fish, potential uses of genetically engineered insects, and DNA microarrays. The ABWG also developed several lecture series for Center scientists on the topics of pharmacogenomics, gene transfer, microarray technology, and nanotechnology, with speakers from FDA, universities, and commercial industries.

The ABWG established a "virtual" library of current texts and reference materials associated with new technologies to share among CVM staff. Once a year, the ABWG holds an open meeting to inform the Center of the group's accomplishments throughout the year as well as new scientific developments in animal technologies.

The ABWG in action

A key role for ABWG members is to serve as a scientific resource for critical and emerging issues for CVM and the agency. They also help to maintain the Center's expertise on these issues through recommendations on staffing and training opportunities.

Members of the ABWG prepare and present talks and posters at multiple scientific conferences in the United States and abroad to communicate the Center's and FDA's processes, findings, and concerns regarding new technologies.

ABWG's outreach can be seen in the activities leading up to the release of CVM's Draft Animal Cloning Risk Assessment on December 28, 2006. Many members of the ABWG played key roles in developing that Draft Risk Assessment.

For example, ABWG members and other CVM staff conducted a review of the available data on the health of animal clones and the safety of food from those animals. This review addresses concerns identified by the National Academy of Sciences in a study commissioned by CVM in 2001 to explore the science-based concerns associated with animal biotechnology, including cloning.

ABWG members also participated in a September 2002 Pew Initiative on Food and Biotechnology symposium, cosponsored by the Center entitled, "Animal Cloning and the Production of Food Products – Perspectives from the Food Chain." The symposium provided a forum for an exchange of perspectives among the various stakeholders in animal cloning: companies that produce and sell clones, animal breeders, processors, retailers, and consumers of foods derived from clones. Members of the ABWG also assisted in the preparations for a Washington Post "Web Chat" on animal cloning in 2002.

The ABWG helps the Center to communicate unfolding regulatory requirements to sponsors developing products and processes using new technologies. The technologies behind new products being investigated are discussed at monthly ABWG meetings to ensure a current and consistent level of knowledge within the Center.

Related to these communication efforts, members of the ABWG helped draft letters that were issued from CVM to all Land Grant Universities on May 14, 2003. The letter reminded university presidents of the need for researchers on campus to establish Investigational New Animal Drug exemptions with CVM to conduct research involving genetic engineering in animal species commonly used for food. Universities need to document plans regarding the disposition of all investigational animals after their participation in the study is completed. University presidents were also reminded that FDA does not permit investigational animals involved in genetic engineering research to be placed into the human or animal food supply without prior authorization.

Members of the ABWG work cooperatively with other FDA centers and Federal agencies. This cooperation allows the ABWG to draw on the experience of other centers and agencies in dealing with new products and processes, such as gene therapy in humans, and bioengineered plants. The ABWG also provides a

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Working Group Keeps CVM Abreast... *(Continued)*

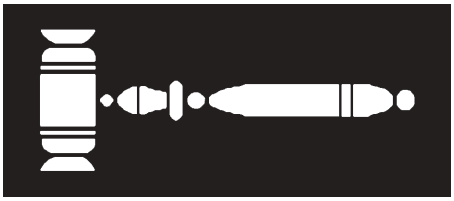
unique perspective to other Centers and agencies in dealing with "cross-cutting" technologies that could involve multiple centers and agencies, such as the use of genetically engineered animals to produce drugs for humans. An example of this cooperative effort is the September 2002 Draft Guidance for Industry entitled, "Drugs, Biologics, and Medical Devices Derived from Bioengineered Plants for use in Humans and Animals." Members of CVM's ABWG worked with scientists throughout FDA and USDA to develop this draft guidance.

Subcommittees within the ABWG study safety questions associated with new technologies, such as potential risks associated with viral vectors, and the risk of allergenicity of foods derived from biotechnology. CVM is represented by ABWG members in agency-wide interest groups focused on specific areas, including genomics, proteomics, and nanotechnology. Participation allows the ABWG to stay abreast of potential new products being developed and to discuss regulatory policies and data issues that may need to be considered. For example, when reviewing new products regulated by FDA, CVM scientists must be familiar with assays and procedures that generate safety and effectiveness data. This allows reviewers to properly evaluate the reliability of these data.

Outlook

New technologies may provide exciting breakthroughs in drug development and how our food is produced. The ABWG will continue to help the Center and FDA stay informed and educated on these new processes, and it will provide scientific leadership and expertise so that new products will be thoroughly evaluated. These efforts will ensure the continued safety of our health, animals, and environment.

Regulatory Activities for February and March 2007



Warning Letters

A WARNING LETTER was issued to Edgar L. Erlanger, president of Nich Marketers, Inc., of Columbus, OH, for marketing adulterated new animal drugs in violation of Section 501(a) of the Federal Food, Drug, and Cosmetic Act (FFDCA). Investigations revealed that the firm was marketing the following animal products that were not the subject of approved new animal drug applications: Sorb-A-Tox Suspension, BIS-CO-SORB Suspension, Aspir-SLO, Colloidal Silver, B-Mune™ Capsules (Beta-1,3-D glucan), Nich UAAGel® (Universal Animal Antidote Gel), and "Tongue to Tail." A review of the firm's Web site showed that several of the products were either labeled or promoted for a variety of animal uses. Some of the products were also found to be misbranded under Section 502 of the FFDCA because the labeling lacked adequate directions for use or a National Drug Control number.

Food adulteration was cited as the basis of a WARNING LETTER issued to James L. Wilson, managing partner, and Cornelius A. Vanderham, partner, of J & D Wilson and Sons Dairy, of Riverdale, CA. Specifically, two animals offered for slaughter as food were adulterated under Sections 402(a) and 501(a) of the FFDCA. Analysis of tissue samples from the first animal by the U.S. Department of Agriculture revealed the presence of flunixin meglumine in the liver at 0.87 parts per million (ppm). A tolerance for this drug in the liver tissue of cattle has been set in 21 CFR 556.286 at 0.125 ppm. Tissue samples of the second animal revealed the presence of penicillin in the kidney at 0.36 ppm. Under 21 CFR 556.510, a tolerance level for residues of penicillin has been established for uncooked edible tissues of cattle at 0.05 ppm. The presence of these drugs in the two animals at those levels rendered the animals adulterated under Section 402(a) of the Act. In addition, the firm was warned that it adulterated the drug flunixin meglumine by failing to use it in conformance with its approved labeling, in that its extralabel use was not in compliance with Section 512(a) of the FFDCA. Similarly, the firm was also warned that it failed to use the drug penicillin-dihydrostreptomycin in conformance with its approved labeling, because the appropriate withdrawal period as set forth in the veterinarian's written instructions was not followed.

Similar warnings were contained in a WARNING LETTER issued to Richard H. Hall, co-owner of Fairmont Farm, Inc., East Montpelier, VT, because of a violation of Section 402(a) of the FFDCA with respect to a slaughtered dairy cow. Sampling by USDA revealed the presence of 0.14 ppm of penicillin in the kidney of the cow, thus exceeding the tolerance of 0.05 ppm established in 21 CFR 556.510. In addition, the firm was warned about adulterating the drug penicillin G procaine because it was

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Regulatory Activities... *(Continued)*

being used extralabel; specifically, the drug was not used on the order of a licensed veterinarian. The drug was used without following the dosage level and duration of treatment for cattle set forth in the approved labeling, thus causing the drug to be adulterated under Section 501(a) of the FFDCA.

Roger and Julie Lanners, owners of a dairy operation in Royalton, MN, received a WARNING LETTER because they offered for slaughter as food three dairy cows that were adulterated under Section 402(a) of the FFDCA. Specifically, tissue samples taken from the first animal revealed the presence of 27 ppm oxytetracycline in kidney tissue, 0.30 ppm sulfadimethoxine in liver tissue, and 0.82 ppm sulfadimethoxine in muscle tissue. Samples of tissues from the second animal revealed the presence of 0.11 ppm ampicillin in kidney tissue. In the third animal, samples taken revealed the presence of 20.98 ppm oxytetracycline in kidney tissue, 6.97 ppm sulfadimethoxine in liver tissue, and 3.88 ppm sulfadimethoxine in muscle tissue. A tolerance of 12 ppm has been established for residues of oxytetracycline in kidney tissues of cattle as codified 21 CFR 556.500. A tolerance of 0.01 ppm has been established for residues of ampicillin in uncooked edible tissues of cattle as codified in 21 CFR 556.40, and a tolerance of 0.1 ppm has been established for residues of sulfadimethoxine in uncooked edible tissue of cattle as codified in 21 CFR 556.640. The presence of these drugs in excess of these amounts in tissues from the animals caused the food to be adulterated. Violations of extralabel use restrictions and proper drug residue withdrawal times were also cited in the WARNING LETTER.

A WARNING LETTER was issued to Arvis, Autic, and Jimmy Loy, president, vice president, and secretary, respectively, of Russell County Stockyards, Russell Springs, KY, because a beef cow and a bull that were offered for sale for slaughter were adulterated under Section 402(a) of the FFDCA. Specifically, tissue samples taken from the two animals revealed residues of the drug gentamicin in the kidneys; no tolerance has been established for residues of this drug in the edible tissues of cattle. During FDA's inspection of the firm, it was also determined that Russell County Stockyards was not obtaining written statements from sellers regarding the medication status of animals it received and not inquiring about the medication status of animals sold at its auctions. Such noncompliance violates Section 301(h) of the FFDCA.

Similar violations were cited in a WARNING LETTER issued to David E. Johnson, d/b/a Joleanna Holsteins, Unadilla, NY. Specifically, the firm consigned a dairy cow to a cattle auctioneer and the cow eventually was slaughtered for human food. USDA's analysis of tissue samples revealed the presence of 0.57 ppm penicillin in kidney tissue and 0.16 ppm penicillin in liver tissue. A tolerance of 0.05 ppm has been established for residues of penicillin in uncooked edible tissues of cattle as codified in 21 CFR 556.510. The excessive residues of penicillin resulted in the food being adulterated within the meaning of Section 402(a) of the FFDCA. Other adulteration warnings were based on the firm's failure to maintain written treatment records to document the identity of the animal, treatment dates, drugs administered, dosage administered, route of administration, and withdrawal times for milk and beef.

Dr. Michael A. Wing of the Meadow Wood Animal Clinic, Cornville, ME, received a WARNING LETTER for causing animal drugs to be unsafe within the meaning of Section 512(a) and adulterated under Section 501(a) of the FFDCA because the drugs were used in a manner that did not conform to their approved applications. In addition, Dr. Wing's actions caused two animals that were slaughtered as food to be adulterated under Section 402(a) of the Act. A tissue sampling of one of the animals in question revealed the presence of residues of flunixin, which had been prescribed by Dr. Wing, in the amount of 3.372 ppm in the liver of a dairy cow. A tolerance of 0.125 ppm flunixin has been established in 21 CFR 556.286. Dr. Wing was also warned about being in violation of the extralabel drug use regulation (21 CFR 530) by not establishing a substantially extended withdrawal period prior to marketing of edible products, and for failure to institute procedures to ensure that the identity of the treated animal or animals is carefully maintained.

Recalls

A Class I firm-initiated recall is ongoing by Wild Kitty Cat Food, Inc., Arundel, ME. The recall involves the following items: (1) Wild Kitty Cat Food-Raw All Natural Chicken with Clam Recipe, Plastic 3.5 oz. (100g) and 16 oz. (1 lb.) units packaged in plastic; (2) Wild Kitty Cat Food-Raw All Natural Duck with Clam Recipe, Plastic 3.5 oz. (100g) and 16 oz. (1 lb.) units packaged in plastic; and (3) Wild Kitty Cat Food-Raw All Natural Tuna with Conch Recipe, Plastic 3.5 oz. (100g) packaged in plastic. The recall was launched because of possible contamination with *Salmonella*, and involves 29,258 3.5-oz. packages, and 3,642 1-lb. packages of the cat food. Distribution of the products affected by the recall is taking place in the following states: Connecticut, Florida, Illinois, Massachusetts, Maryland, Maine, Michigan, New Mexico, New Jersey, New York, and Washington.

A Class II firm-initiated recall is ongoing by Pfeifer Arno, Inc., Greenbush, WI, of bulk cattle feed made with recalled Darling's 85% Blood Meal, Flash-Dried. The blood meal used to make the recalled cattle feed was itself recalled because it was cross-contaminated with prohibited bovine meat and bone meal that had been manufactured using common equipment, and labeling

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Regulatory Activities... *(Continued)*

did not bear the cautionary BSE statement. The recall involves 42,090 lbs. of feed that was limited to distribution in Wisconsin.

Rangen, Inc., Buhl, ID, has completed a Class II recall of almost 1 million pounds of feed products manufactured from bulk feed containing blood meal that was cross-contaminated with prohibited meat and bone meal, and the labeling did not bear the cautionary BSE statement. Distribution of the recalled products was limited to Idaho and Nevada.

A firm-initiated Class II recall is ongoing by Protient, Inc., Saint Paul, MN, involving 90,000 lbs. of Utah Proteins (the manufacturer) Sweet Dairy Whey (Edible Grade) held in paper bags with a polyethylene liner. The recall is being carried out because one of the whey powder ingredients may be contaminated with *Salmonella*. Distribution was limited to California, Nevada, and Utah.

A Class II firm-initiated recall has been completed by Eatonton Co-Op Feed Co., Eatonton, GA, involving its dairy cattle feed blends containing ProLak and/or ProAmino II protein concentrate that was manufactured in April 2006. The recall, which involved 25 tons of material, was carried out because the finished feed product was manufactured from raw feed material that may have been contaminated with ruminant-derived protein. Distribution was limited to Georgia.

Golden Rod Feed Mill, Inc., of Cullman, AL, has completed a firm-initiated Class II recall of 52,500 lbs. of Broiler Grower, 200-118-101, medicated bulk poultry feed that contained excessive amounts of sodium. Distribution of the product was limited to Alabama.

A Class II recall is ongoing by Darling National LLC of Omaha, NE, involving 1.36 million pounds of its Bulk Darling's 85% Blood Meal, Flash Dried, distributed in totes and 1-lb. bags. Distribution took place in Wisconsin, Texas, Tennessee, Nebraska, Colorado, and Minnesota. The product is being recalled because some of the exempt bovine blood meal was cross-contaminated with prohibited bovine meat and bone meal that had been manufactured on common equipment, and the labeling did not bear the cautionary BSE statement that it should not be fed to ruminants.

A Class II recall is ongoing by Belcher Pharmaceuticals, Inc., of Largo, FL, involving 88,120 bottles of Thyroxine L (Levothyroxine Sodium Tablets, as well as Oral Solution, USP) (Veterinary). The products are being recalled because processing and cleaning procedures were not validated prior to production, and the products had some GMP failures related to the quality system. Distribution of the products in question was limited to Missouri.

Comings and Goings

New Hires

OFFICE OF THE DIRECTOR

- Michael Zimmerman, Consumer Safety Officer

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Stephanie Bowman, Staff Fellow
- Sudesh Kamath, Staff Fellow

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Neal Bataller, Director of Compliance

OFFICE OF RESEARCH

- Karen Blickenstaff, Microbiologist

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Kendra Biddick, Consumer Safety Officer
- H. Gregg Claycamp, Supervisory Risk Assessment Manager

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Lowell Fried, Consumer Safety Officer, Deceased

Approvals for February and March 2007

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

ADVANTAGE MULTI™ (imidacloprid 10% and moxidectin 2.5%) (NADA 141-251) and ADVANTAGE MULTI™ (imidacloprid 10% and moxidectin 1%) (NADA 141-254), filed by Bayer HealthCare LLC, Animal Health Division. The first NADA provides for the veterinary prescription use of ADVANTAGE MULTI™ for dogs and is a topical solution used for the prevention of heartworm disease, the treatment of flea infestations, and

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Approvals for February and March 2007 *(Continued)*

New Animal Drug Applications (Continued)

the treatment and control of several internal parasites. The second NADA provides for the veterinary prescription use of ADVANTAGE MULTI for cats and is a topical solution used for the prevention of heartworm disease, the treatment of flea infestations, and the treatment and control of ear mites and several internal parasites. Notice of approval was published March 9, 2007.

- CERENIA™ (maropitant citrate) Tablets (NADA 141-262), filed by Pfizer, Inc. The NADA provides for the veterinary prescription use of maropitant citrate tablets in dogs for the prevention of acute vomiting and for the prevention of vomiting due to motion sickness. Also approved is Pfizer's NADA 141-263 for CERENIA™ Injectable Solution, used by veterinary prescription in dogs for the prevention and treatment of acute vomiting. Notice of the approvals was published March 1, 2007.

- RECONCILE® (fluoxetine hydrochloride) Chewable Tablets (NADA 141-272), filed by Elanco Animal Health, a division of Eli Lilly & Co. The NADA provides for the veterinary prescription use of RECONCILE® Chewable Tablets for the treatment of canine separation anxiety in conjunction with a behavior modification plan. Notice of approval was published February 12, 2007.

- 35% PEROX-AID® (hydrogen peroxide) (NADA 141-255), filed by Eka Chemicals, Inc. The NADA provides for the use of 35% PEROX-AID® to control mortality in freshwater-reared finfish eggs due to saprolegniasis, to control mortality in freshwater-reared salmonids due to bacterial gill disease associated with *Flavobacterium branchiophilum*, and to control mortality in freshwater-reared coolwater finfish and channel catfish due to external columnaris disease associated with *Flavobacterium columnare (Flexibacter columnaris)*. Notice of approval was published February 6, 2007.

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

- BAYTRIL® 100 (enrofloxacin) Injectable Solution (NADA 141-068), filed by Bayer Healthcare LLC, Animal Health Division. The product is approved for the treatment of bovine respiratory disease associated with several bacterial pathogens. The supplemental NADA provides for changing a pathogen name from *Pasteurella haemolytica* to *Mannheimia haemolytica* on product labeling. Notice of approval was published March 9, 2007.

- SYNANTHIC® (oxfendazole) Bovine Dewormer Suspension 22.5% and SYNANTHIC® (oxfendazole) Bovine Dewormer Suspension 9.06% (NADA 140-854), filed by Fort Dodge Animal Health, Division of Wyeth. This supplemental NADA was approved for oral use over-the-counter of SYNANTHIC in cattle for the removal of various internal parasites. Notice of approval was published March 9, 2007.

- PANACUR® (fenbendazole) Paste (NADA 120-648), and SAFE-GUARD® (fenbendazole) Paste (NADA 132-872), filed by Intervet, Inc. The first supplemental NADA provides for the use of PANACUR® (fenbendazole) Paste in horses for the control of various internal parasites, while the second one provides for the safe use of SAFE-GUARD®

(Continued, next page)

Approvals for February and March 2007 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

(fenbendazole) Paste in cattle for the control of various internal parasites. The supplemental NADAs provide for a revised human food safety warning on product labeling. Notice of the two approvals was published March 9, 2007.

- ZILMAX® (zilpaterol hydrochloride 4.8%) (NADA 141-258), filed by Intervet, Inc. The supplemental NADA provides for the use of ZILMAX® (zilpaterol hydrochloride 4.8%) Type A medicated article to formulate Type B and Type C medicated cattle feeds. The supplemental NADA provides for the removal of a caution statement against the formulation of pelleted feeds from labeling. Notice of approval was published March 1, 2007.

- COBAN® 60 and COBAN® 90 (monensin, USP) (NADA 38-878), filed by Elanco Animal Health, a Division of Eli Lilly & Co. The supplemental NADA provides for use of COBAN® 60 and COBAN® 90 (monensin, USP) Type A medicated articles in the feed of chickens. The supplement provides for minor revisions to labeling. Notice of approval was published March 1, 2007.

- REVALOR-XS (trenbolone acetate and estradiol) (NADA 141-269), filed by Intervet, Inc. The supplemental NADA provides for the use of REVALOR-XS (trenbolone acetate and estradiol), an ear implant, for increased rate of weight gain and improved feed efficiency in steers fed in confinement for slaughter. The product was assigned over-the-counter status by FDA. The approval qualifies for 3 years of marketing exclusivity beginning on the date of approval; notice of approval was published February 15, 2007.

- BOVATEC 91 (lasalocid) Type A medicated article (NADA 138-993), filed by ADM Alliance Nutrition, Inc., Quincy, IL. The supplemental NADA provides for the use of lasalocid to make MooMan's® Cattle Mineral BT, a free-choice mineral Type C medicated feed for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, and dairy and beef replacement heifers). The supplement provides for the use of a lasalocid Type A medicated article containing a 20-percent lasalocid activity per pound. Notice of approval was published February 2, 2007.

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

- HEIFERMAX® 500 (melengestrol acetate) Liquid Premix, OPTAFLEXX® (ractopamine hydrochloride), and RUMENSIN® (monensin sodium) single-ingredient Type A medicated article (ANADA 200-448), filed by Ivy Laboratories. The ANADA provides for the use of these products to make dry and liquid, three-way combination drug Type C medicated feeds for heifers fed in confinement for slaughter. The ANADA is approved as a generic copy of Elanco Animal Health's NADA 141-234 for combination feed use of MGA® 500, OPTAFLEXX®, and RUMENSIN®. Notice of approval was published March 8, 2007.

- GENTAMICIN SULFATE TOPICAL SPRAY (gentamicin sulfate, USP, with betamethasone valerate, USP) (ANADA 200-415), filed by First Priority, Inc. The ANADA provides for the use of gentamicin sulfate with betamethasone valerate on dogs for the treatment of infected superficial lesions caused by bacteria sensitive to gentamicin. First Priority's

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Approvals for February and March 2007 *(Continued)*

Abbreviated New Animal Drug Applications (Continued)

Gentamicin Sulfate Topical Spray is approved as a generic copy of Schering-Plough Animal Health Coprporation's GENTOCIN® Topical Spray, approved under NADA 132-338. Notice of approval was published February 6, 2007.

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

COMPONENT® TE-200 with TYLAN® (trenbolone acetate and estradiol with tylosin tartrate) (ANADA 200-346), filed by Ivy Laboratories, a Division of Ivy Animal Health, Inc. The product is a subcutaneous implant used for increased rate of weight gain and improved efficiency in steers and heifers fed in confinement for slaughter. The supplemental ANADA provides for the addition of a pellet containing 29 milligrams tylosin tartrate to the approved COMPONENT® TE-200 implant. Notice of approval was published March 1, 2007.

NOROMECTIN® (Ivermectin) Pour-On (ANADA 200-272), filed by Norbrook Laboratories, Ltd. The supplemental ANADA adds claims for persistent effectiveness of Noromectin Pour-On for Cattle to control infections and protect against re-infection with the following internal and external parasites: *Oesophagostomum radiatum* and *Dictyocaulus viviparus* for 28 days after treatment; *Cooperia punctata* and *Trichostrongylus axeia* for 21 days after treatment; *Ostertagia ostertagi*, *Haemonchus placei*, *Cooperia oncophora*, and *Cooperia surnabada* for 14 days after treatment; and *Damalina bovis* for 56 days after treatment. The effect of the supplement is to add claims that are no longer protected by 3 years of marketing exclusivity that expired on November 24, 2006. Notice of approval was published February 12, 2007.

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