FDA VETERINARIAN

Center for Veterinary Medicine

May/June 2003 Vol. XVIII, No. III

New CDC Web Site for Animal/Human Health Risks

The following article is used with permission, and provides information about human health risks related to animals. Veterinarians may wish to duplicate this article and provide copies to their interested clients. As always, material that appears in the ***FDA Veterinarian*** *is free of copyright and may be reproduced without permission.*

The U.S. Centers for Disease Control and Prevention (CDC) has created a web site to provide people with information about the health-related risks of owning and caring for animals. Links are located throughout the web site for general information about companion and wild animals and the diseases they could carry. The web site offers important information about safe practices for handling domestic animals and avoiding wild ones. The Healthy Pets, Healthy People web site is online at *www. cdc.gov/healthypets*.

By following CDC's simple tips on the Healthy Pets, Healthy People web site, you can enjoy your pets while protecting yourself against diseases they carry. Because wild animals can carry diseases that are dangerous to people, CDC discourages direct contact with wildlife. You should never adopt wild animals as pets or bring them home. Teach children never to handle unfamiliar animals, wild or domestic, even if the animals appear to be friendly.

To prevent illness due to animal contact, the Centers for Disease Control and Prevention recommends the following for all people, but especially for those at greatest risk of getting sick from pets:

- Always wash your hands thoroughly with soap and running water after contact with animals and their feces.
- Avoid rough play with cats and dogs to prevent scratches and bites.

A person's age and health status may affect his or her immune system, increasing the chances of getting sick. These people include:

- Infants and children less than 5 years old
- Elderly
- Pregnant women
- People undergoing treatments for cancer
- People who have received organ transplants
- People with HIV/AIDS.

(Continued, next page)

National Pet Week
May 4 - 10, 2003

"Pets Make the Difference"

In This Issue

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

FDA/CVM Final Rule Streamlines Adverse Event Reporting

FDA/CVM has issued a final rule reducing FDA's requirements for records and reports concerning experiences with approved new animal drugs. The final rule, published in the March 31, 2003, *Federal Register*, significantly reduces both reporting and record keeping requirements concerning experiences with New Animal Drug Applications (NADA) and Abbreviated NADAs (ANADA), as compared with current regulations, and incorporates many of the industry comments on earlier drafts.

This final rule clearly defines the kinds of information to be maintained and submitted by new animal drug applicants for an NADA or ANADA. It revises the timing and content of certain reports to enhance their usefulness. It provides for the protection of public and animal health, and reduces the record keeping and reporting requirements. Dr. Glenn Peterson, CVM Team Leader of the Marketed Products Information Team, noted that "applicants will now be able to petition FDA to change the frequency of reporting their yearly drug experience reports (DER's), which should reduce their reporting to CVM." This final rule is effective June 30, 2003.

Additional information about the final rule may be found in the March 31, 2003, *Federal Register* (*http://www.fda.gov/OHRMS/DOCKETS/98fr/03-7475.html*) or by contacting Dr. Glenn Peterson, Center for Veterinary Medicine (HFV-212), FDA, 7500 Standish Place, Rockville, MD 20855, 301-827-0224, *gpeterso@cvm.fda.gov*.

New CDC Web Site for Animal/Human Health Risks *(Continued)*

If you fit into one of the groups of people outlined above, you should avoid contact with the following animals:

- Reptiles (turtles, lizards, and snakes)
- Baby chicks and ducklings
- Puppies and kittens less than 6 months old
- Pets with diarrhea

Photo by Karen Kandra

CDC discourages direct contact with wildlife, such as these fox cubs.

CVM Launches Spanish-Language Page

To help provide Spanish speakers with vital information, FDA's Center for Veterinary Medicine (CVM) has launched a new section on our Home Page that includes links to CVM publications in Spanish. This new page, "Publicaciones en Español del Centro de Medicina Veterinaria (CVM)" may be viewed at: *http://www.fda.gov/cvm/index/spanish_ pubs/CVMEspanol.htm*.

The documents on this new page include two fact sheets about FDA's role in safeguarding animal health to protect consumers and keeping the U.S. free of bovine spongiform encephalopathy (BSE.) In addition, there are links to four small entities compliance guides on FDA's ruminant feed (BSE) rules. These are FDA guidance documents #67 "Small Entities Compliance Guide for Renderers," #68 "Small Entities Compliance Guide for Protein Blenders, Feed Manufacturers, and Distributors," #69 "Small Entities Compliance Guide for Feeders of Ruminant Animals with On-Farm Feed Mixing Operations," and #70 "Small Entities Compliance Guide for Feeders of Ruminant Animals without On-Farm Feed Mixing Operations."

Any comments or suggestions on the page should be directed to Ms. Deborah Brooks at *dbrooks@cvm. fda.gov*.

FDA VETERINARIAN

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Comments are invited.

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7519 Standish Place
Rockville, MD 20855

How FDA Regulates Veterinary Devices

FDA has regulatory oversight over veterinary medical devices[1] and can take appropriate regulatory action if a veterinary device is misbranded, mislabeled, or adulterated.

FDA **does not require** submission of a 510(k) or formal pre-market approval for devices used in veterinary medicine. It is the responsibility of the manufacturer and/or distributor of these articles to assure that these animal devices are safe, effective, and properly labeled.

Device manufacturers who exclusively manufacture, or distribute veterinary devices are not required to register their establishments and list veterinary devices. Firms that manufacture radiation-emitting devices **do** need to register their products under the radiological health regulations, administered by the Center for Devices Radiological Health (CDRH) (*www.fda.gov/cdrh*).

FDA recommends that manufacturers and/or distributors of veterinary medical devices request a review of their product labeling and promotional literature to ensure that it complies with labeling and regulations. This includes devices marketed in another country and offered for importation into the U.S. A review may be requested by forwarding complete labeling, including any instruction manuals, promotional literature, and diagrams or photographs, to the following address (do not send actual devices):

Food and Drug Administration
Center for Veterinary Medicine
Division of Compliance (HFV-230)
7500 Standish Place
Rockville, MD 20855

Although the Quality Systems Regulations published in Title 21, *Code of Federal Regulations* (CFR), Part 820, apply to human devices only, FDA recommends that veterinary device manufacturers become familiar with these regulations and be guided by them in manufacturing/assembling their device articles. Title 21 CFR, Part 800 to 1299 deals with the regulations governing medical devices. Copies may be purchased from the Superintendent of Documents, U.S. Government Printing Office, Mail Stop: SSOP, Washington, DC 20402-9328. See *http://www.access.gpo.gov/su_docs/index.html*.

Adulterated or Misbranded Devices

Animal devices which are not safe, effective, and properly labeled are deemed to be adulterated and/or misbranded under the Act. Examples of when something may be considered adulterated or misbranded:

- If it has been prepared, packed, or held under insanitary conditions whereby it may have been contaminated with filth, or whereby it may have been rendered injurious to health (adulteration). §501(a)(2)(A)
- If its labeling is false or misleading in any particular (misbranding). §502(a)
- If its labeling fails to bear adequate directions for use (misbranding). §502(f)(1)

  Adequate directions for use means directions by which the layman can safely use the device. Those devices which, because of the nature of the device itself or because they are for use in a condition which requires the training and expertise of a veterinarian and thus for which adequate directions for lay use cannot be written, are prescription devices. These devices must be labeled with the veterinary prescription legend "Caution: Federal law restricts this device to sale by or on the order of a licensed veterinarian," and they must be used under the supervision of a licensed veterinarian.
- If it is dangerous to health when used in accordance with its label directions (misbranding). §502(j)

Devices not in compliance with the Act may be subject to seizure, and firms and individuals responsible for marketing these illegal devices may be subject to other penalties of the Act, such as fines and even imprisonment.

Devices not in compliance with the Act may be subject to seizure, and firms and individuals responsible for marketing these illegal devices may be subject to other penalties of the Act, such as fines and even imprisonment.

Dental Devices

Any product that bears a claim to affect the dental health of an animal through a mechanical rather than a chemical action on the teeth and/or gums is a dental device. Such a product might be a nylon or rubber bone. Because of the abrasive action of these products on the teeth, they do help to clean the teeth of dogs. Therefore, at this time FDA would not object to these products being labeled with claims for helping to clean the teeth of dogs and marketed, provided there is no safety problem for the animal.

Dental devices that are labeled with claims for the prevention and/or treatment of dental disease such as gingivitis and periodontal disease would be considered of higher regulatory priority. These products may be subject to regulatory action under the Act if marketed.

The following veterinary medical devices have received regulatory attention in the past:

(1) Electronic dog collars which would emit an electrical shock when the dog barked. These collars were found to be dangerous because they caused burns to the animal and

(Continued, next page)

CVM Scientists Win Awards

At the FDA Science Forum, held April 24-25, 2003, in Washington, DC, the following CVM scientists were recognized:

EXCELLENCE IN ANALYTICAL SCIENCE

CAMPYLOBACTER WORKING GROUP

Robert D. Walker, M.S., Ph.D., Patrick F. McDermott, M.S., Ph.D., Sonya M. Bodeis, B.S.

For the development of the National Committee for Clinical Laboratory Standards (NCCLS) approved antimicrobial susceptibility testing method for fastidious food borne bacterial pathogen Campylobacter jejuni.

Different species of *Campylobacter* have been recognized as human pathogens for several decades with *Campylobacter jejuni* being the most common. It has been estimated that approximately 2.4 million cases of campylobacteriosis occur every year in the U.S. The development of a standardized susceptibility testing method for *Campylobacter*, including a validated quality control strain, will provide scientists worldwide with accurate and reliable data. The advancement made by the awardees will accelerate understanding of the genetic mechanisms involved in *Campylobacter* drug resistance. It will enable researchers to quantify the contribution different resistance determinants underlying the evolution of antimicrobial resistance in this organism. This type of research will, in turn, form the basis for developing new antimicrobials for treating infections caused by *Campylobacter*. A single reliable testing method will also allow researchers and policy makers to more accurately evaluate the effectiveness of older antibiotics, by monitoring changes in antimicrobial susceptibility over time. Improved surveillance will enable policy makers to better identify sources of resistant organisms infecting humans and animals, and implement intervention strategies to limit their spread. In addition, the standardized agar dilution test will serve as a reference point for developing appropriate interpretive criteria and for validating other *Campylobacter* testing methods both within the United States and internationally. Towards this end, the CVM scientists have been teaching the method to microbiologists from human and veterinary State diagnostic laboratories, and research institutions, including governmental institutions, from the United States and Mexico.

EXCELLENCE IN REVIEW SCIENCE

Harlan J. Howard, Ph.D.

For leadership in creating scientific standards, where none existed previously, in evaluating effectiveness and animal safety for reproductive agents used in food animals.

Photo by Eric Dubbin

Dr. Harlan J. Howard

Dr. Howard's efforts, direction, and leadership have established current scientific standards for reproductive products in livestock species by approving new products for existing claims (e.g., estrous synchronization) and novel reproductive claims. Establishment of these standards provides the template that personnel from FDA/CVM and the regulated industry can follow for appropriate study design and for conduct of effectiveness and animal safety studies. The public benefits from these approvals and novel approaches because food is produced more economically which keeps food affordable and increases profits for farmers. Animal health benefits because synchronized estrus produces a uniform offspring crop that will be vaccinated, dewormed, fed and processed in a way that maximizes the health and well-being of the animal.

How FDA Regulates Veterinary Devices *(Continued)*

could be activated by other noises, including other dogs barking.

(2) "Cold Laser" devices were found to be misbranded because they could not achieve the therapeutic effects they claimed.

(3) Pulsed magnetic wave therapy devices were found to be misbranded because they were making excessive therapeutic claims for many more conditions than scientific studies could support.

In addition, electronic veterinary devices, which emit radiation, are subject to the Radiation Control for Health and Safety Act, which has various performance and safety standards.

[1] The Federal Food, Drug, and Cosmetic Act (the Act) defines medical devices as *"an instrument, apparatus, implement, machine, contrivance, implant, in-vitro reagent, or other similar or related article, including any component, part, or accessory thereof, which is intended for use in the diagnosis of disease or other conditions; in the cure, mitigation, treatment, or prevention of disease in man or other animals; or which is intended to affect the structure or any function of the body of man or other animals."* Further, a device *"does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals, and is not dependent upon being metabolized for the achievement of any of its principal intended purposes."* Examples of devices include such things as needles, syringes, surgical instruments, prosthetic devices, X-ray equipment, certain diagnostic test kits, and dental appliances.

Poster Awards

CVM is pleased to announce the following winners of the 2003 Science Forum poster awards. Dr. Linda Youngman, Director, Office of Research, made the announcement following the 9th Annual FDA Science Forum adding that, "although we are a relatively small Office and Center, we received significant accolades for our ongoing work. It is very gratifying that the research conducted by OR is so highly regarded by our scientific colleagues."

SIGMA XI POSTER AWARDS 2003

1. **POSTER & CATEGORY O-07.** ***Systemic and Local Drug Delivery Inhibits Vascular Stenosis Following Angioplasty and Grafting: Safety and Effectiveness and Routes of Administration.***

   J.W. Karanian, N. Kipshidze, D. Wray-Cahen, S.L. Hilbert, A. Ashby, W.F. Pritchard – *CDRH*

Swine studies were designed to assess the safety and effectiveness of systemic versus local administration of drugs to inhibit vascular occlusion due to stenosis. Stenosis resulting from neointimal hyperplasia is a typical failure mode associated with balloon angioplasty, stenting and vascular grafting. Scientists have shown balloon anigioplasty of swine coronary arteries is followed by the development of stenosis (neointimal hyperplasia) by 30 days. Systemic estrogen replacement therapy (ERT) was shown to moderately reduce the angioplasty-induced coronary stenosis in swine. Recent reports analyzing the risks/benefits of ERT have focused on chronic systemic administration, not localized single dose delivery. However, scientists have shown that local delivery of an immunosuppressent drug markedly inhibits stenosis at the venous anastomosis of a vascular graft. They are currently studying the pharmacokinetics and pharmacodynamics of local drug delivery (e.g., steroid, immunosuppressent and cytostatic drug) as a method of reducing the neointimal hyperplasia that leads to vascular stenosis in our swine models. These results are consistent with the proposition that local drug delivery, via an intraluminal catheter or drug-eluting device, may provide a more safe and efficacious therapy for the treatment of occlusive vascular disease.

2. **POSTER & CATEGORY F-15.** ***Microbial Source Tracking (MST) of Foodborne Salmonella & Campylobacter.***

   R. Singh, S.L. Foley, D.G. White, S. Zhao, S. Simjee, P.F. McDermott, R.D. Walker – *CVM*

Approximately 76 million people suffer from foodborne illnesses in the U.S. annually at an average cost to the U.S. economy of $15 billion. Many pathogenic bacterial species have been implicated in foodborne diseases, with infections caused by *Salmonella* and *Campylobacter* species occurring at higher frequencies than those caused by other species. In this study scientists present MST as a means of determining the food animal of origin of *Campylobacter* and *Salmonella*. They have investigated serotyping, antimicrobial susceptibility, pulse-field gel electrophoresis (PFGE) and multilocus sequence typing (MLST) for their capacities to distinguish *Campylobacter* and *Salmonella* isolates from pigs, cattle, turkey, and chickens. For *Campylobacter*, preliminary analysis of the data suggests that PFGE and MLST provide better discriminatory power than biochemical profiles or serotyping. For *Salmonella,* serotyping appears to be the best method for certain strains, namely *S.* Dublin and *S.* Choleraesuis isolates, in which over 99% are from cattle and swine, respectively. The results from this study could aid in determining the food animal species from which *Salmonella* or *Campylobacter* may have originated. Further, the methods can be used as an example for future MST studies of other foodborne pathogens. Data from these studies will aid the FDA's ability in making science-based regulatory decisions about food safety.

CLEAR SCIENCE COMMUNICATION AWARDS 2003

1. **POSTER & CATEGORY A-29.** ***Validation of Methods to Confirm Chloramphenicol at 0.1 ppb in Shrimp, Crabmeat and Honey: Collaboration between FDA CVM, FDA ORA, Florida Dept of Agriculture and Consumer Affairs and the Canadian Food Inspection Agency.***

   M.C. Carson, C. B. Nochetto, D.N. Heller, K. Ferbos, P.J. Kijak – *CVM & ORA*

Chloramphenicol (CAP) is a potent and cheap antibiotic that is associated with aplastic anemia and other toxic effects in humans. It is banned from use in food-producing animals in the U.S. Low levels of CAP were detected by analysts in Europe, Canada, and some U.S. States in imported shrimp, honey, and other commodities. Existing FDA methods could only detect 1-2 parts per billion CAP. In July 2002 the Commissioner committed the FDA to begin analyzing imported foods with methods capable of confirming CAP at 0.3 ppb, consistent with enforcement levels used in other countries, and also consistent with the claimed detection limits of marketed screening assays. FDA needed to quickly validate methods to confirm CAP at sub-part per billion concentrations. The Florida Department of Agriculture and Consumer Services and the Canadian Food Inspection Agency had recently developed appropriate LC-MS-MS methods for shrimp and honey, respectively, which they shared with the FDA. CVM validated Florida's method to confirm 0.1 ppb CAP in shrimp and crabmeat, and validated Canada's method to confirm 0.1 ppb CAP in honey. CVM scientists adapted FDA's shrimp method (LIB 4284) for analysis on a triple quadrupole, lowering its limit of confirmation from 1 ppb to 0.1 ppb, and validated the modified method.

CVM is proud of its staff members and congratulates all FDA award winners.

International Activities

Denmark Meeting Addresses Animal Feeding

The Codex Alimentarius Commission is responsible for making proposals to the Directors-General of the Food and Agricultural Organization and the World Health Organization on all matters pertaining to the implementation of the Joint FAO/WHO Food Standards Program. The purpose of these programs is to protect the health of consumers and ensure fair trade practices.

The 4th Session of the ad hoc Intergovernmental Codex Task Force on Animal Feeding was held in Copenhagen, Denmark, from March 25th through the 28th and was hosted by the Government of Denmark and chaired by Mr. Mogens Nagel Larsen, Director or the Danish Plant Directorate. The Session was attended by 129 participants from 41 Member countries, and 15 international organizations. CVM's Director, Dr. Stephen Sundlof was the U.S. delegate, and he was supported by Dr. Dan McChesney of CVM, and Mr. Larry Miller, and Ms. Edith Kennard of USDA. The Task Force was able to complete its work and forwarded the proposed draft Code of Practice on Good Animal Feeding to the 26th Session of the Codex Alimentarius Commission for final adoption at Steps 5/8 (with the omission of Steps 6 and 7).

The full procedure for the elaboration of a Codex Standard encompasses 8 steps. The step process ensures that all member countries will have adequate opportunities to comment and discuss the proposed Code before it is accepted at Step 8 by the Commission. Completing the 8-step process can take several years. This Working Group has worked for 4 years and prior to the Working Group being established, other Committees had made attempts to address the issue of good animal feeding practices since 1995.

The participating member countries were able to agree on compromise wording for the newly reviewed Sections 5, 6 and 7. The Task Force's work in this area was aided greatly by the working group established after the June 2002 meeting and charged to re-draft these Sections. The working group succeeded in getting and sharing input from several countries prior to the meeting such that there was general agreement on these Sections and the Task Force only needed to resolve issues that were often system or country specific.

Sections 1 through 4 of the draft Code had been reviewed in June 2002 and agreement had been reached on most paragraphs. The discussion in these Sections was focused by Mr. Larsen to four areas that contained bracketed text. Re-wording and adding words addressed the concerns in two of the bracketed text areas. The other two areas, the definition of feed additive, and GMO labeling, proved to be extremely difficult to agree upon and were only resolved when the Chairman declared that agreement had been reached.

The issue with the feed additive definition was the phrase "improves animal performance." The U.S., Canada, Australia, and New Zealand argued that the inclusion of the phrase was not proper because that claim is covered under the Codex definition of veterinary drug. After extended discussion lead by the EU delegation, the Chairman determined that the phrase would be dropped. The EU delegation protested and may take the issue to the Codex Alimentarius Commission in June.

The subject of labeling products of new technologies, and particularly, GMO products was intensely debated. Several countries wanted mandatory labeling while others opposed mandatory labeling. Many groups pointed out that requiring labeling of feed or feed ingredients without requiring the labeling of food from the animals made no sense. Compromise wording was proposed that would let the competent authority in each country determine whether a product of new technologies should be labeled as a risk management measure after conducting a risk assessment. The wording is, "Competent authorities may decide that feed and feed ingredients consisting, containing, or produced from GMOs should be labeled with references to the genetic modification as a risk management measure." Debate ensued and the Chairman finally determined that agreement had been reached. The U.S., Canada, and Australia requested that the record of the meeting specifically state that they had opposed the compromise wording. Dr. Dan McChesney, Deputy Director of CVM's Office of Surveillance and Compliance believes that "even though there was disagreement on some issues, overall the delegates thought the information contained in the Code was beneficial and would further the goal of protecting the health of consumers."

Finally, new items for work in the animal feed area were proposed by the International Dairy Foundation and the European Union. Agreement on the areas for new work could not be reached. It was agreed that Mr. Larsen would mention all of these areas in his report to the Commission. □

International Activities *(Continued)*

Food Safety Discussed in New Zealand

CVM's Deputy Director, Dr. Linda Tollefson described the Food Safety Quad meeting as "an excellent opportunity to discuss food safety issues of importance to all the participating countries." She added, "This year's meeting was particularly relevant to U.S. concerns because we focused on counter-terrorism efforts and what each country was doing to address these new threats."

The 12th Session of the Quadrilateral Meeting on Food Safety (Australia, Canada, New Zealand, USA) met in Queenstown, New Zealand, March 17 - 20.

The U.S. delegation was led by USDA's Under Secretary for Food Safety, Dr. Elsa Murano. USDA representation included the FSIS Deputy Administrator Linda Swacina, Karen Stuck and Karen Hulebak, also of FSIS, and Ed Scarbrough of the U.S. Codex office. FDA representation included Dr. Cathy Carnevale, Mr. Lou Carson, and Dr. Mike Wehr, CFSAN, and Dr. Linda Tollefson, CVM.

The 12th Food Safety Quad meeting provided opportunity for updates on current food safety activities of the Quad countries, and allowed participants to develop strategies to resolve mutual food safety issues and concerns.

The 12th session concentrated on developing the Quad countries' perspectives on supporting an OIE/Codex interface, particularly for food safety issues involving zoonotic diseases, antimicrobial resistance, and risk analysis. The representatives agreed to support further development of the interface at the Codex General Principles meeting. The countries agreed to keep each other informed on emergency response preparations undertaken in each country and other counter-terrorism issues. There was a great deal of discussion by Canada, New Zealand, and Australia on FDA's proposed regulations implementing the food/feed safety provisions of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002, including registration of food/feed facilities, prior notice of imported food, and administrative detention.

The Codex Ad-Hoc Intergovernmental Task Force on Foods Derived from Biotechnology had met in Japan the week prior to the Quad meeting. The Task Force has been extended to include issues concerning transgenic animals and cloning so each of the quad countries discussed their country's approach to regulating these areas. Agreement was reached to continue these discussions and share risk assessments and other scientific information as it is developed. The Quad countries also agreed to support an Expert Consultation on antimicrobial resistance to be convened by FAO/WHO/OIE and to encourage the consultation to be held as soon as is feasible.

FDA Seeks VMAC Consumer Representative

FDA is requesting nominations for a consumer representative to serve as a voting member on its Veterinary Medicine Advisory Committee (VMAC.) Nominations will be accepted through December 31, 2003. FDA has a special interest in ensuring that women, minority groups, and individuals with disabilities are adequately represented on advisory committees and, therefore, encourages nominations of qualified candidates from these groups.

All nominations should be sent to Michael Ortwerth, Advisory Committee Oversight and Management Staff (HF-4), FDA Office of the Commissioner, 5600 Fishers Lane, Rockville, MD 20857, e-mail:

Michael.Ortwerth@fda.gov.

Persons nominated for membership on the committees as a consumer representative must: (1) Demonstrate ties to consumer and community-based organizations; (2) be able to analyze technical data; (3) understand research design; (4) discuss benefits and risks; and (5) evaluate the safety and efficacy of products under review. The consumer representative must be able to represent the consumer perspective on issues and actions before the advisory committee, serve as a liaison between the committee and interested consumers, associations, coalitions, and consumer organizations, and facilitate dialogue with the advisory committees on scientific issues that affect consumers.

All nominations must include a cover letter, a curriculum vitae or resume (which should include nominee's office address, telephone number, and e-mail address), and a list of consumer or community-based organizations for

(Continued, next page)

Think Twice Before Using Gentamicin

by Linda Cline

No one was thinking about drug residues when they treated several hundred head of sick young calves that had just traveled hundreds of miles from dairy farms in Idaho and Washington. They were just trying to keep them alive and save their sight, because many were scouring and suffering with severe pinkeye. Using gentamicin under a veterinarian's direction seemed to be the most effective treatment when given orally to treat the scours and used as a flush in the calves' eyes. The calves recovered and in another two months were in good enough shape to be shipped out to feedlots.

Another year would pass before the calves had grown and reached market weight. No one was thinking about drug residues when the calves, now grown to steers, were shipped for slaughter, because no one had treated them at the feedlot. Sampling by USDA at the slaughter plant changed everyone's thinking when a gentamicin residue was found in the kidney of the steer sampled.

Photo by Karen Kandra

Gentamicin is not approved for use in cattle

There is no "tolerance" for gentamicin in cattle, because a gentamicin-containing drug has not been approved for use in cattle. Gentamicin is known to bind to the kidney tissue of cattle

(Continued, next page)

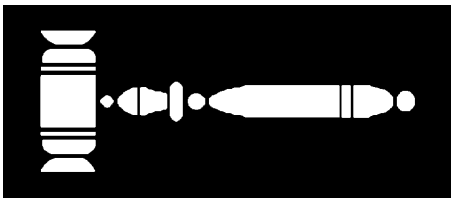
FDA Seeks VMAC Consumer Representative *(Continued)*

which the candidate can demonstrate active participation.

Any interested person or organization may nominate one or more qualified persons for membership on the VMAC to represent consumer interests. Self-nominations are also accepted. FDA will ask the potential candidates to provide detailed information concerning such matters as financial holdings, employment, and research grants and/or contracts to permit evaluation of possible sources of conflict of interest. The nomination should specify that this is for the Veterinary Medicine Advisory Committee. The term of office is up to 4 years, depending on the appointment date.

Regulatory Activities

by Karen A. Kandra



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

- Juan I. Echeverria, Owner, Echeverria Dairy, Chino, CA
- Avelino A. Vieira, Owner, Alvieira Dairy, Wendell, ID

The above violations involved illegal residues of penicillin in a culled dairy cow and tilmicosin in a downer cow.

A warning letter was issued to Ettore Alosio, President, Micelle Products, Inc., Lake Forest, CA, for violations concerning the distribution of unapproved animal drugs, including, Arthamine Advanced, Arthramine Plus, Anti-Gas, Champ Chewable Nutritional Pebbles, Calmative, Dermaplex, and Dermasol spray/gel.

Because these products are not approved under a New Animal Drug Application, they are unsafe under Section 512 of the Federal Food, Drug, and Cosmetic Act (the Act) and adulterated under Section 501(a)(5) of the Act.

Under Section 201(g) of the Act, any article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals" or "intended to affect the structure or any function of the body of man or other animals" is regarded as a drug.

Think Twice Before Using Gentamicin *(Continued)*

irregardless of the route of administration and could be a residue concern for 18 months or more. In fact, ***no withdrawal period*** has been scientifically established in cattle for those veterinarians searching the literature for direction in an "extra-label" use scenario. No one thought about a drug being sustained in an animal for a year or more, but gentamicin is different and professionals treating cattle need to know this. In this investigation, veterinarians involved in treating the calves recommended a six-month withdrawal period and their colleagues were their source of the withdrawal period. There was a learning experience from this investigation for the professionals involved when they were informed of the unusual residue problems with gentamicin, and subsequently stopped using it in dairy and feedlot cattle.

CVM's Dr. Mike Talley notes that "veterinarians and producers should be aware that there are approved drugs to treat the conditions described in calves that have much less potential for prolonged residues available for extra-label use if the approved drugs were found not to be effective by the prescribing veterinarian. In addition, the American Association of Bovine Practitioners (AABP), the American Veterinary Medical Association (AVMA), and the Academy of Veterinary Consultants have position papers or resolutions saying that aminoglycosides should not be used for extra-label purposes in cattle."

Linda Cline is a FDA Investigator in the Sioux City, Iowa Resident Post.

Freedom of Information

The Freedom of Information Act (FOIA) allows anyone to request copies of records not normally prepared for public distribution. FOIA pertains to existing records only and does not require agencies to create new records to comply with a request. It also does not require agencies to collect information they do not have or to do research or analyze data for a requestor. In addition, FOIA requests must be specific enough to permit an FDA employee who is familiar with the subject matter to locate records in a reasonable period of time.

How to Make a FOI Request

All FOIA requests must be in writing and should include the following information:

a. Requestor's name, address, and telephone number.

b. A description of the records being sought. The records should be identified as specifically as possible. A request for specific records that are releasable to the public can be processed much more quickly than a request for "all information" on a particular subject. Also fees for a more specific and limited request will generally be less. Information on major information systems maintained by FDA can be obtained by using the *Department of Health and Human Services Government Information Locator Service (GILS) site*. This information may be useful in narrowing a request.

c. Separate requests should be submitted for each firm or product involved.

d. A statement concerning willingness to pay fees, including any limitations.

All FOIA requests must be in writing. FDA does not accept FOIA requests sent via e-mail. Requests should be mailed to the following address:

Food and Drug Administration
Office of Information Resources Management
Division of Freedom of Information (HFI-35)
5600 Fishers Lane
Rockville, MD 20857

Or requests may be sent via fax to: (301) 443-1726. If there are problems sending a fax, call (301) 443-2414.

Fees

FOIA requestors may have to pay fees covering some or all of the costs of processing their request. Requestors may want to include the maximum dollar amount they are willing to pay. If the fees exceed the maximum amount stated, FDA will contact the requestor before filling the request. Requestors are generally billed for fees after their requests have been processed; however, if total fees are expected to exceed $250.00 FDA may require payment in advance of processing.

Effective March 26, 2003, the hourly rate for FOI search and review time has been increased as follows:

- GS-1 through GS-8 – $18.00 per hour ($1.00 increase)
- GS-9 through GS-14 – $36.00 per hour ($2.00 increase)
- GS-15 and above – $64.00 per hour ($3.00 increase)

Leveraging Examples in CVM – Part V: Interagency Agreements

by David B. Batson, Ph.D.

Introduction

This is the fifth in a series of articles on leveraging activities in FDA's Center for Veterinary Medicine (CVM). This article will define interagency agreements, when they can be used and how these agreements can be used as leveraging tools for addressing important research/regulatory questions facing the Center.

The purpose of an interagency agreement is to provide a mechanism for project collaboration and the transfer of funds between two Federal agencies. This agreement involves collaboration to eliminate duplication of effort and extend overall consumer protection through use of the collective resources. It could also involve sharing knowledge, personnel, property, facilities and equipment that would strengthen programs of mutual concern in the public interest. If FDA receives funds from and provides services to another agency this collaborative arrangement is referred to as a reimbursable interagency agreement. Before an agreement is signed by FDA, it may have to be cleared, depending on the subject matter, through (1) the Research Involving Human Subjects Committee, (2) the Associate Commissioner for Regulatory Affairs, (3) the Office of Resources Information Management, (4) the Office of Planning and Evaluation, (5) the Office of Human Resources and Management Services and/or the Institutional Animal Care and Use Committee. The clearances are the responsibility of the sponsoring FDA office. The sponsoring office is also responsible for the scientific peer review of the data from these scientific research efforts.

The FDA has been involved in highly successful interagency agreements with agencies such as the United States Department of Agriculture (USDA), the Centers for Disease Control and Prevention (CDC), the Veterans Administration, the U. S. Army, and the U.S. Geological Survey. Examples of these agreements are described below.

National Antimicrobial Resistance Monitoring System

The National Antimicrobial Resistance Monitoring System (NARMS) was established in 1996 as a collaborative effort among three Federal agencies, FDA, USDA, and CDC. The NARMS program monitors changes in susceptibilities of human and animal enteric bacteria to 17 antimicrobial drugs.

Bacterial isolates are collected from human and animal clinical specimens, from healthy farm animals, and from the raw products of food-producing animals. The objectives of the program include: (1) provide descriptive data on the extent and temporal trends of antimicrobial susceptibility in *Salmonella* and other enteric organisms from human and animal populations, (2) facilitate the identification of resistance in humans and animals as it arises, and (3) provide timely information to veterinarians and physicians. The ultimate goal of this program is to prolong the lifespan of approved drugs by promoting prudent and judicious use of antimicrobial drugs and to identify areas for more detailed investigation.

NARMS is composed of two separate components for testing the susceptibility of animal and human isolates. These isolates are submitted by 17 State and local Departments of Health to either CDC or USDA. Isolates derived from human patients are submitted for testing to CDC, Atlanta, Georgia. Bacterial isolates of animal parts are submitted for testing to USDA, Athens, Georgia. Animal and human isolates currently monitored in NARMS are non-typhoid *Salmonella*, *Campylobacter*, *E. coli*, and *Enterococci*. In addition, human isolates are monitored for *Salmonella typhi*, *Shigella* Spp., *Listeria monocytogenes* and *Vibrio* Spp. Additional information on the NARMS program is available at *http://www.fda.gov/cvm/index/narms/narms_pg.html*.

Use of Tissue-Fluid Correlations to Predict Drug Residue Levels in Edible Tissues from Food-Producing Animals

In 2001 FDA entered into a reimbursable interagency agreement with USDA's Food Safety and Inspection Service (FSIS) (1) to investigate the correlation of drug levels in biologic fluids such as urine, saliva or blood, with residues that are present in edible tissues, e.g., meat, liver or kidney, (2) to develop and validate physiologic models to enable food safety personnel to accurately predict, prior to slaughter, whether a particular animal has tissue drug residues which are violative of the approved tolerances, and (3) to develop these models by correlating drug levels in some easily sampled biologic fluids, e.g., urine, saliva or blood, with drug

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. . . Interagency Agreements *(Continued)*


Photo by Dr. Renate Reimschuessel

A non-invasive collection of urine is made from a Holstein steer to assay for drug residues.

residues that are present in edible tissues. These models may also be useful for back extrapolating an estimate of the dose administered and the time of administration based on a measured concentration in tissue.

The testing for drug residues in tissues from food-producing animals normally occurs after slaughter. As a result, edible tissues with residues that exceed tolerance are declared adulterated and must be destroyed. The analytical methods used to measure these residues in tissues are time-consuming to perform and less than 1% of the slaughtered animals are monitored for drug residues. This approach is inefficient and economically costly for both consumers and producers, and does not provide assurance of optimal food safety. The use of rapid, inexpensive preslaughter screening tests, similar to those used for milk, based on detection of drug residues in some easily obtainable biological fluid (saliva, plasma or urine) would enable monitoring of more animals and help ensure greater food safety. Preslaughter testing also allows animals with violative residues to be held back until such time as drug residues deplete to safe levels by normal routes of excretion.

The pharmacokinetics of a number of agents are characterized by tissue distribution studies and subsequent physiologically-based modeling. These models are useful in predicting tissue levels at certain times after initial or multiple dosages. By evaluating the relationship between drug administration, tissue uptake, and, more importantly, tissue elimination, one can better predict if an animal is likely to have tissue residues which exceed tolerances. The investigators will assess the tissue exposure by developing physiologically-based pharmacokinetic flow models characterizing tissue distribution and elimination of the test agents. In addition to providing insight on tissue distribution and disposition, these physiological flow models can also assist in extrapolating results in one animal species to another. For additional information on this study please contact Keesla Moulton, Ph. (301) 827-8054.

Real-Time Monitoring for Toxicity Caused by Harmful Algal Blooms and Other Water Quality Perturbations

FDA entered into a reimbursable interagency agreement with the U.S. Army at Fort Detrick, MD, in collaboration with the University of Maryland, in 1999 to provide the public and public officials with real-time information on developing toxic conditions in ambient water that may be caused by harmful algal blooms or other sources of water quality degradation. Such information is quite valuable for protecting the public from direct exposure to toxins in the water as well as an early warning system for bioaccumulation of toxin. The objective was accomplished through the use of an automated biomonitoring system that tracks the ventilatory and movement patterns of fish.

Harmful algal blooms, including those associated with toxicity, have been increasing in frequency, intensity, and severity in U.S. coastal areas. Recently, the Mid-Atlantic region has experienced blooms of *Pfiesteria* and *Pfiesteria*-like organisms leading to fish kills that have damaged local fisheries and to concerns about potential effects on people exposed while engaged in sport or commercial

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. . . Interagency Agreements *(Continued)*

fishing, swimming, or other water-related recreational activities. The risks of consuming exposed fish are currently unknown but are of concern due to the fact that numerous other dinoflagellate toxins accumulate in the food chain. Unfortunately, the public and environmental decision-makers may not learn that an algae-related fish kill is underway until large numbers of dead or dying fish are observed, so the availability of early warning information on developing toxic conditions in susceptible waters is critical. The information generated by this project was beneficial to FDA by providing insight into the monitoring for algal blooms. Since many of these cause foodborne toxicity, such a monitoring system is quite valuable. In addition, the data benefits commercial fisheries, recreation industries, and the general public. Health and environment officials can use these data, in real time, to advise these sectors on the safety of waters in terms of potential exposures to harmful algal blooms. Additional information may be obtained by contacting Dr. Renate Reimschuessel (Ph. 301-827-8025).

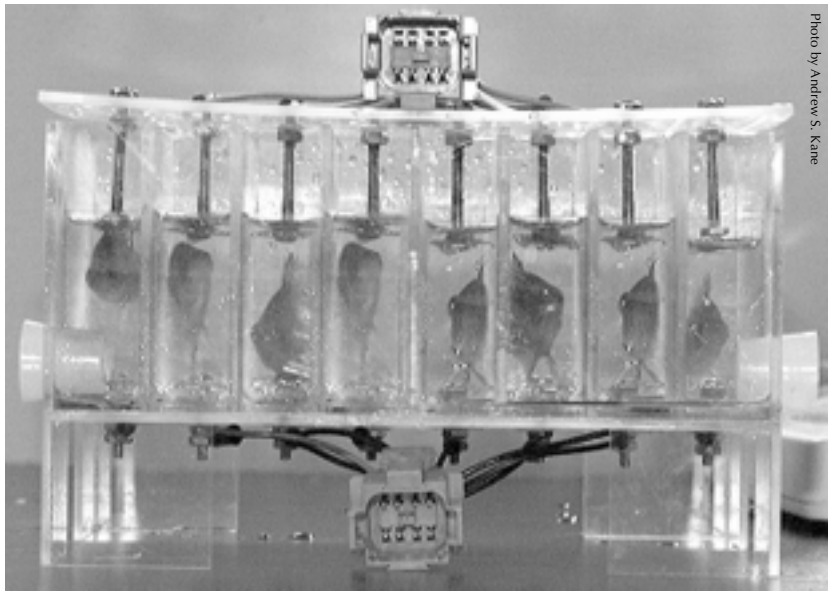

Photo by Andrew S. Kane

Bank of 8 flow-through biomonitoring chambers. Note the set of electrodes above and below the fish connected to their respective wiring harnesses. These electrodes non-invasively pick up weak electrical impulses and transmit them through an amplifier to a computer, where the sine wave responses are deciphered into the VR, VD, CR and %Mov endpoints by software algorithms.

Concluding Comments

The collaborations formed through these projects allowed the Center to leverage and expand its on-going program by partnering with outside organizations, including other Federal agencies. These collaborations permit the Center to utilize outside scientific expertise, facilities, and equipment to address regulatory and research questions before the Center. Although these particular projects were between FDA and other government agencies, it is possible for individuals and organizations outside of the government to submit proposals based upon projects consistent with the mission of CVM. Therefore, if you have questions on any of the Center's interagency agreement projects, leveraging in general, or if you have an interest in initiating a collaboration with FDA's Center for Veterinary Medicine please contact David Batson at (301) 827-8021 or David Lynch at (301) 827-5337.

The next and final installment in this series will be titled "Where Do We Go From Here?" This final article will provide suggestions on the development of collaborative research ideas and subsequent steps for initiating new leveraging opportunities with the FDA.

Dr. Batson is a Health Scientist Administrator in CVM's Office of Research.

CVM Warns of Dioxin in Mineral Mixes

FDA is alerting firms manufacturing mineral mixes and mineral premixes for use in animal feed that minerals that are by-products or co-products of industrial metal production may contain dioxin.

Recently, FDA found that some of these by-products or co-products contained high levels of dioxin. In March 2002, FDA requested a recall of chelated minerals and mineral premixes because of high levels of dioxin. In the 2002 case, the source of the dioxins was related to the high temperature process used in making the chelated minerals. The Agency believes that in the current case the process used to

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Ask CVM

The CVM Home Page receives quite a bit of mail. Starting with this issue, the ***FDA Veterinarian*** *will feature samples of the types of inquiries that come in to the Home Page and how CVM responds to them. The questions and answers featured here are composites of multiple questions we have 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 reported an adverse drug reaction to CVM by submitting a ***"Veterinary Adverse Experience, Lack of Effectiveness or Product Defect Report"*** *(Form FDA1932a). How can I get a copy of the form I sent in for my records?*

You can obtain a copy of the report you submitted by filing a Freedom of Information (FOI) request. Instructions for filing an FOI request are on the Internet at *www.fda.gov/cvm/efoi/efoi.html*. Please be sure to include as much detail as possible in your request.

I am trying to find a list of FDA restricted drugs for food animals, where would I find it?

There is a list of drugs that are prohibited from use in food animals outside of the specified label uses. These drugs are:

- Chloramphenicol
- Clenbuterol
- Diethylstilbestrol (DES)
- Dimetridazole
- Ipronidazole
- Other nitroimidazoles
- Furazolidone
- Nitrofurazone
- Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine)
- Fluoroquinolones
- Glycopeptides

Additionally, use of drugs other than as specified on the label is not allowed except under the order of a licensed veterinarian within a valid veterinarian-client-patient relationship. Extra-label use of drugs in treating food-producing animals for improving rate of weight gain, feed efficiency, or other production purposes, or for routine disease prevention is prohibited under the Animal Medicinal Drug Use Clarification Act. See **FDA and the Veterinarian** on our Home Page for more details *http://www.fda.gov/cvm/index/fdavet/fdavet00.html#Anchor-Extr-15584*

How can I find out if a drug is approved for use in dogs?

A listing of drugs approved for animal use in the U.S. can be found in the Green Book on the Internet at *http://www.fda.gov/cvm/greenbook/greenbook.html*. You can search the Green Book by the name of the drug, approved species, indications, ingredients, dose forms, trade names, or sponsor name.

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CVM Warns of Dioxin in Mineral Mixes *(Continued)*

produce brass resulted in the dioxin contamination of zinc oxide. FDA will be actively checking these and similar products for dioxin.

Dioxins are ubiquitous, low level environmental contaminants. With cumulative exposure, they are potential carcinogens and may cause reproductive or developmental health problems. Environmental sources of dioxin pollution have been markedly reduced over the past decade. The result has been a significant reduction in overall dioxin exposure to the public. Presently, the primary source of human exposure to dioxins is through food.

Earlier this year, FDA's food and feed surveillance programs detected elevated levels of dioxin in a feed and traced the dioxin to a mineral component of that feed. The implicated zinc oxide and zinc oxide premixes that were used in livestock, aquaculture, and poultry feed contained extremely high levels of dioxin. A recall of these products and feed containing the zinc oxide has been implemented. An additional mineral component (copper oxide) is also being investigated as a possible source of dioxin. Both mineral components currently under investigation are reclamation products from industrial metal production.

FDA's public health objective is to reduce the level of exposure to dioxin in the animal and human foods by finding and stopping sources of added dioxin from entering the food supply.

FDA's public health objective is to reduce the level of exposure to dioxin in the animal and human foods by finding and stopping sources of added dioxin from entering the food supply. To further reduce public exposure to dioxins, FDA will continue its food and feed surveillance programs, and continue investigating whether other products from industrial metal production that are used as feed ingredients are a source of dioxin.

Firms or individuals that have questions about this subject may contact Ms. Gloria Dunnavan, Division of Compliance, Center for Veterinary Medicine at 301-827-1168.

Ask CVM *(Continued)*

We are looking into marketing dietary supplements for animals in the U.S. What can we say on the label about such supplements in terms of any benefits, claims, etc.?

Please be advised that if your product is a drug i.e., *"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,"* it will need to be the subject of an approved new animal drug application before it can be sold. This also includes articles intended for use as a component of a drug.

Information on filing a new animal drug application can be found at *http://www.fda.gov/cvm/index/other/nadaappr.htm*. If your product is a feed you can find information at *http://www.fda.gov/cvm/index/animalfeed/animalfeed.htm*

You can find information about labeling of pet food products at *http://www.fda. gov/cvm/index/animalfeed/petfoods.htm*. You may also find helpful information in "Interpreting Pet Food Labels—Special Use Foods" at *http://www.fda.gov/cvm/index/consumer/labelint.htm*

There is also an article about animal dietary supplements in the *FDA Veterinarian http://www.fda.gov/cvm/index/fdavet/2002/May_June.htm#Update*

CVM Comings and Goings

In an effort to keep our readers apprised of new personnel developments, we will report new hires, retirements, and resignations of CVM personnel.

APRIL HIRES

Kristen Anderson/Microbiologist/ONADE – Ms. Anderson reviews new animal drug applications in the Division of Manufacturing Technologies.

New Animal Drug Approvals

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 141-201)	Laidlomycin (Cattlyst®), Chlortetracycline (Aureomycin)	Cattle. For improved feed efficiency, increased rate of weight gain, treatment of bacterial enteritis, control of bacterial pneumonia.	**MEDICATED FEED**—The NADA provides for the use of approved, single-ingredient Type A medicated articles containing laidlomycin and chlortetracycline to formulate two-way combination drug Type C medicated feeds for cattle fed in confinement for slaughter. Depending on the proportions used the medicated feeds are used for improved feed efficiency, increased rate of weight gain, treatment of bacterial enteritis caused by *Echerichia coli*, and control of bacterial pneumonia caused by *Pasteurella multocida* organisms. *Federal Register* 03/21/03

Supplemental New Animal Drug Approvals

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 107-996)	Lasalocid (Avatec), Bacitracin Methylene Disalicylate (BMD)	Chickens. For the prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	**MEDICATED FEED**—The supplemental NADA provides for a zero-day withdrawal period for the use of approved two-way combination drug Type C medicated feeds containing lasalocid and bacitracin methylene disalicylate in broiler and fryer chickens. *Federal Register* 03/31/03

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Supplemental New Animal Drug Approvals *(Continued)*

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Schering-Plough Animal Health Corp. (NADA 141-177)	Gentamicin sulfate, Mometasone furoate, Clotrimazole (Mometamax™) RX	Dogs. For treatment of otitis externa.	**OTIC**—The supplemental NADA provides for the addition of once-daily administration to the dosage regimens for gentamicin/mometasone/clotrimazole otic suspension used to treat otitis externa in dogs. *Federal Register* 03/31/03
Novartis Animal Health, Inc. (NADA 141-203)	Deracoxib (Deramaxx™) RX	Dogs. For the control of pain and inflammation.	**ORAL**—The supplement provides for veterinary prescription use of deracoxib chewable tablets for the control of pain and inflammation associated with osteoarthritis. *Federal Register* 04/17/03

Abbreviated New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Phoenix Scientific, Inc. (ANADA 200-342)	Pyrantel Pamoate	Horses and ponies. For the removal and control of certain internal parasites.	**ORAL**—The approved ANADA is a generic copy of Pfizer's Strongid approved under NADA 129-831. *Federal Register* 03/20/03

Supplemental Abbreviated New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Intervet, Inc. (ANADA 200-075)	Salinomycin (Sacox®)	Chickens, quail. For the prevention of coccidiosis.	**MEDICATED FEED**—The supplement provides for use of a salinomycin Type A medicated article to make Type C medicated feeds used for the prevention of coccidiosis in roaster and replacement (breeder and layer) chickens and for the prevention of coccidiosis in quail. *Federal Register* 02/11/03
Phoenix Scientific, Inc. (200-123)	Oxytetracycline (Maxim 200)	Lactating dairy cattle, swine. Treatment of various bacterial diseases.	**SUBCUTANEOUS or INTRAMUSCULAR**—The supplement provides for the administration of this oxytetracycline injectable solution to lactating dairy cattle. *Federal Register* 02/20/03

Food Additive Petition Approval

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
BASF Corp. (FAP 2250)	Conjugated Linoleic Acid (CLA)	Swine. Source of fatty acids.	**ORAL**—The petition is to amend the food additive regulations in Food Additives Permitted in Feed and Drinking Water of Animals (21 CFR Part 573) to provide for the safe use of conjugated linoleic acid (CLA) as a source of fatty acids in swine diets at levels not to exceed 1 percent in complete feed. *Federal Register* 03/11/03

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