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FDA VETERINARIAN

NATIONAL PET WEEK 2001

During the week of May 6 – 12, veterinarians, veterinary technicians, and pet owners will celebrate "People and Pets, The Perfect Combination." National Pet Week 2001 is sponsored by the American Veterinary Medical Association (AVMA), the Auxiliary to the AVMA, the American Animal Hospital Association, and the North American Veterinary Technician Association. The theme recognizes the warmth, joy, love, and companionship that pets bring into our lives as well as the vital role of the veterinarian in that relationship.

Today's pets are considered important members of the family, and for many persons pets provide emotional stability and improve their quality of life. Just as human medicine is making huge advancements to increase people's life expectancy, sophisticated medical procedures are now available for pets. Veterinarians are increasingly referring patients to animal cardiologists, oncologists, ophthalmologists, and dermatologists for special treatment to ensure a longer, more comfortable life.

Pet ownership is a long-term commitment, but the rewards will last a lifetime.

In the photo at left, Targa, 13, and Kenneth, 89, are constant companions.

□

ELDERLY DOGS DESERVE SPECIAL ATTENTION

by Karen A. Kandra

The following article provides information about caring for elderly dogs. 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.*

With advancements in veterinary medicine and nutrition, pets are living longer than ever before. Geriatric medicine is gaining in popularity as the demand grows for more attention to our aging pet population.

Most dogs are considered "old" around eight or nine years. Large and giant breeds are considered middle-aged around 6 or 7. Smaller breeds tend to live much longer than large breeds, even into their mid-teens.

Canine senior citizens have more needs, and require more attention. Their sight and hearing may diminish, and they will require more sleep and move more slowly. Stairs may become a hardship, so sleeping arrangements may need adjusting. They need to go out more often, as bladder and bowel control may weaken with age. They still need appropriate exercise, frequent grooming, and proper nutrition. Since they may have fewer teeth, a soft diet may be necessary.

(Continued, next page)

In This Issue

U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION CENTER FOR VETERINARY MEDICINE

Most changes with the aging process occur gradually, but there are several things to watch for, and preventative steps to take to ensure that your favorite dog will keep active and healthy into his/her golden years. Regular veterinary examinations are critical to a dog's health. It is important to keep a detailed medical history and continue regular veterinary visits to ensure a long, healthy life for your dog.

Obesity is a major problem with dogs in our society, since owners tend to feed table scraps in excess. Serious health problems may result from obesity. Extra weight puts a strain on the animal's heart, lungs, skeleton, and muscles, and lowers resistance to disease. Regular moderate exercise and proper nutrition are essential to maintain optimal weight and health.

Arthritis often affects older dogs, and causes them to slow down and lessens their ability to climb steps or jump up on a favorite chair. If your dog shows signs of arthritis, your veterinarian can examine him and may suggest radiographs. Your veterinarian then may be able to prescribe an appropriate medication to lessen the pain, and give the dog more mobility.

Heart disease is more common in aging dogs. Initial signs are coughing, shortness of breath, rapid breathing, and even fainting spells. If diagnosed in the early stages, medications are available to treat the symptoms of heart disease that can help your dog live a more normal life.

Your dog will benefit from regular grooming to stimulate the coat and skin. During grooming sessions, check for skin disorders or dry, irritated skin, or oozing sores under the coat. This is a good time to notice any lump or growth that has appeared. Often these are benign growths, but may require surgery, especially if they are growing. Your veterinarian can help guide you with these decisions.

Bathing is only suggested on rare occasions, since frequent baths remove natural protective oils from the skin. If he is dirty, or shows evidence of fleas, he may be bathed in lukewarm water using mild shampoo. Be sure to rinse the soap thoroughly. Also look for parasites that may cause discomfort. Fleas are common, but can be controlled by oral medication or topical products, including powders, sprays, collars, or dips. Contact your veterinarian for recommended prevention or treatment.

Eyes should be cleaned of any discharge with a soft cloth moistened with water or saline solution. Ear discomfort is indicated by scratching or head shaking. Infections can settle deep in the ear canal and should be treated by your veterinarian immediately.

The dog's mouth should be examined periodically for signs of gum disease, and tartar accumulation. This is an important part of the annual veterinary examination, and any problems should be addressed immediately. Many older dogs lose their teeth, or they may be extracted if disease or infection is detected.

Elderly dogs may exercise less frequently on hard surfaces to keep their nails filed down, so it is your job to clip their nails, to keep them comfortable. Neglected nails may cripple a dog.

Preventing Accidents

Extra precautionary measures should be taken with elderly dogs. As their hearing and eyesight diminishes, they should be supervised more closely, and not allowed to fend for themselves. They may not see or hear cars or life-threatening hazards. Do not allow them on balconies, or stairwells without supervision.

Keep poisons out of reach of any animal. Many popular household plants can be toxic to dogs, including cyclamen, ferns, philodendrons, dieffenbachia, and other varieties. Cleaning solutions such as detergents, bleaches, oven cleaners, etc. may pose hazards as well. Make sure bottle caps are tight and the rags used to apply these chemicals are stored safely out of reach. Treat pets like children and keep medicines locked up, and never leave candy, especially chocolate, where dogs may have access to it.

Outdoor hazards include windshield cleaners, antifreeze, weed killers, used motor oil, and insecticides. Antifreeze has a sweet taste, and just a few licks can be fatal to your dog. Other hazards include rodenticides used to kill rats and mice. If any poisoning occurs, call your veterinarian immediately, and provide a sample of the poison with the labeling to aid in proper treatment. In an emergency, you may wish to call the ASPCA Animal Poison Control Center at 1-888-426-4435.

Avoid extremes in temperature. Of course, never leave any dog in a

(Continued, next page)

FDA Veterinarian

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ELDERLY DOGS DESERVE SPECIAL ATTENTION (Continued)

parked car in hot weather, even with the windows open, and never leave him outside without water and shade. Similarly, in frigid temperatures, bring him indoors, and be sure he always has shelter from wind, rain, and sun, even in mild temperatures. Tolerance for temperature extremes is reduced with old age, and you should always consider the dog's comfort. In old age, you may not want to take your pet on car trips as often, since he may become uncomfortable with strange places, and would rather stay at home in an environment where he is very familiar.

YOUR VETERINARIAN IS THE BEST SOURCE OF INFORMATION ABOUT ALL ANIMAL HEALTH MATTERS.

In a medical crisis situation, call your veterinarian immediately if you detect any of the following symptoms:

- abnormal breathing
- abnormal behavior
- active bleeding
- bone exposure
- puncture to abdomen, chest, or neck
- watery or bloody discharge
- partial or complete paralysis
- difficulty urinating
- profuse vomiting or diarrhea
- poison ingestion
- bloated or tender abdomen
- rectal temperature over 103 degrees F or under 99 degrees F
- dehydration
- abnormal color of gums or eyes
- disorientation
- collapse

NEVER GIVE ANY MEDICATION (EVEN ASPIRIN) WITHOUT CONSULTING YOUR VETERINARIAN.

Together you and your veterinarian can have a positive influence on your dog's happiness and comfort and ensure that the quality of life is maintained during the senior years. A lifetime of love should be rewarded with special attention.

Karen Kandra is a Consumer Safety Officer in CVM's Office of Management and Communications, and Editor of the ***FDA Veterinarian****.* □

OFFICE OF RESEARCH 2000 HIGHLIGHTS

Introduction

The Office of Research (OR) is the laboratory-based research arm of the Center for Veterinary Medicine (CVM), Food and Drug Administration (FDA). OR's research priorities are ever-changing, being driven by the needs of other CVM offices—i.e., the Office of New Animal Drug Evaluation (ONADE) and the Office of Surveillance and Compliance (OSC), and by FDA-wide requirements to thoroughly assess the latest food safety concerns. To meet these needs, the Office of Research is staffed by researchers with diverse scientific backgrounds—microbiology, biochemistry, toxicology, analytical chemistry, pharmacology, etc., as well as scientists with specialist training, e.g., aquatic science specialists and antimicrobial resistance geneticists.

To give the reader an idea of the broad array of research studies conducted by OR scientists, this section briefly describes some of OR's recent studies. These studies are organized below by the three OR Divisions in which they were conducted—DRC, DAR and DAFM.

CVM's Office of Research, Laurel, MD

Division of Residue Chemistry (DRC)

OR's Division of Residue Chemistry (DRC) has been responsible for developing, validating and monitoring methods used in FDA's highly-effective milk safety programs. More recently, DRC has been focused on developing methods to measure antibiotic residues in various tissues. They also have been conducting surveys to examine possible misuse of antibiotics, particularly fluoroquinolones, to prevent the emergence of antibiotic-resistant bacteria.

Depletion of OTC in Shrimp

DRC scientists provided the analytical support needed to complete an oxytetracycline (OTC) residue depletion study in collaboration with Dr. Rodney Williams at the University of Arizona. Currently, OTC is not approved for use in shrimp feed. Moreover, since shrimp aquaculture

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is a relatively small market in the U.S., it is unlikely that drug sponsors would invest resources necessary for a New Animal Drug Application (NADA) permitting OTC use in shrimp aquaculture. A producer consortium has been generating the data necessary for a NADA.

Dr. Philip Kijak analyzed the OTC-medicated shrimp food and found that it contained 4.5 g OTC-HCl/ kg feed. Drs. Mary Carson and Maureen Ngoh analyzed shrimp tissue from the OTC-depletion study, using an HPLC method validated at OR. Shrimp were fed the medicated diet for 14 consecutive days, and then switched to a control diet for OTC-withdrawal. The results indicated that OTC residues in medicated shrimp had fallen below FDA's tolerance of 2 ppm (for tetracycline residues in human food) by 48 hours post-withdrawal of medication. The results of this study will be used to support INAD 8069 for OTC use in shrimp.

Cow-Calf Model for Mother-Child Studies

DRC has also developed a cow-calf model which predicts drug transfer rates from mother to infant. The model can be used to monitor drug transfer via the placenta and milk. Data from cow-calf model studies will be used to predict similar drug transfers in a human mother and child. This model has been used to demonstrate that normal dosing of ivermectin (a lipid soluble drug) to the cow leads to an unanticipated accumulation of drug in the calf. A similar accumulation of lipid soluble drug might be anticipated in a nursing infant of a drug-treated mother. Data from the cow-calf model studies, supported by an FDA Office of Women's Health grant, can be used to predict drug accumulations in mother's milk for human infants. DRC's animal data will also be critical in the design of human drug transfer studies.

Fluoroquinolones in Eggs of Laying Hens

DRC scientists recently conducted a series of studies to determine if fluoroquinolone (FQ) residues are transferred into eggs of laying hens and, if so, which biomarker, the parent compound or its metabolites, is most suitable for surveys. ^{14}C-sarafloxacin was orally administered to six laying hens for five consecutive days. Eggs were collected for 15 days after initial drug treatment. Egg yolk and egg albumen were separated and assayed for total radioactive residues (TRR). Radioactivity was detected in egg yolk and egg albumen on the second day of dosing and reached a maximum at 24 hours after drug withdrawal. Thereafter, the sarafloxacin TRR levels in egg albumen declined rapidly and were undetectable two days after the last dose while levels in egg yolk declined at a much slower rate and were undetectable seven days after drug withdrawal. In both the egg albumen and egg yolk, HPLC analysis indicated that the parent sarafloxacin was the major component. Thus, the parent compound was used in the nationwide survey for FQ in eggs of laying hens.

DRC's next challenge was to develop a multiresidue HPLC method for the determination of three FQs: sarafloxacin, enrofloxacin, and ciprofloxacin in table eggs. In the U.S., sarafloxacin and enrofloxacin are approved for use in broiler chickens and in turkeys for the treatment of bacterial infections, but they are not approved for use in laying hens. Ciprofloxacin is a human drug but is prohibited for use in animals; it was included in the method development because it is a metabolite of enrofloxacin.

Finally, in collaboration with CVM statisticians, DRC scientists designed and conducted a national survey for FQs in table eggs. The objective was to identify possible illegal use of FQs thereby helping to ensure that the U.S. egg supply is safe. With the help of FDA's Office of Regulatory Affairs (ORA), 276 eggs were sampled from 75 egg production or distribution firms throughout the United States. Because the radiotracer study indicated that drug residues stay in the egg yolk for a longer time than in the egg albumen and that egg yolk is a better matrix of choice for monitoring, we conducted our assays on egg yolk only. Of the 276 eggs assayed, none were found to be positive for FQs. Results from this study suggest that illegal use of fluoroquinolones in laying hens is not a widespread phenomenon, and provide support for CVM's poultry drug NOOH that there is no evidence of FQ misuse in laying hens.

Division of Animal Research (DAR)

The Division of Animal Research (DAR) has been heavily involved in conducting an array of animal food safety studies. Some noteworthy research accomplishments by DAR personnel in recent years are outlined below.

BSE: Method for Detection

In an attempt to prevent the emergence of bovine spongiform encephalopathy (BSE) in U.S. beef cattle, FDA established a ban on most ruminant materials in feed for ruminant animals. However, CVM did not have an analytical method to detect bovine materials in animal feed. Thus, Dr. Michael Myers optimized a polymerase chain reaction (PCR) method for this purpose. DAR scientists then conducted a multi-laboratory method validation trial that showed the PCR method to be specific and reliable in detecting the presence or absence of bovine materials in animal feed. The PCR test is also rapid and will save time thus ensuring that critical Agency resources are focused on possible violations of the feed additive ban.

Drug Bioequivalence Testing

According to current CVM policy, companies introducing a new generic drug must demonstrate bioequivalence to the pioneer product in every target animal species (thus requiring multiple investigations, 20 animals/species, for each new drug). Traditionally it has been

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thought that product bioequivalence cannot be extrapolated across target animal species. However, in response to a request from ONADE, DAR scientists examined the validity of extrapolating parental product bioequivalence using two injectable formulations of ampicillin in calves, sheep, and swine. Employing products recognized to be bioinequivalent provided an opportunity to detect species differences. Marked interspecies differences were noted clearly defining the need for further research before current CVM bioequivalence policy can be changed.

Preventing Violative Neomycin Residues in Calves

Violative residues of neomycin in cattle tissues, especially calves, have long been a concern for CVM. Thus, DAR scientists developed a program of research to investigate the transfer of neomycin into tissues of young calves. Results from this program demonstrated that neomycin was absorbed by both ruminating and, to a greater extent, in non-ruminating calves. Other research demonstrated that neomycin levels in kidneys depleted to below tolerance levels at 21 days post-withdrawal of a medicated milk replacer. Further OR investigations examined depletion of neomycin in kidneys following oral administration of the approved DESI dosage of neomycin in cattle. These studies provided critical information necessary to preventing violative neomycin residues in calves.

Division of Animal and Food Microbiology (DAFM)

Currently, one of the FDA's most important tasks is to ensure the safety of foods from microbial hazards—particularly from antibiotic-resistant bacteria. The increase in the incidence of human infections caused by these resistant pathogens has raised growing concerns for therapeutic failures in animals and humans. The President's Food Safety Initiative has provided CVM with funding to support research of antimicrobial resistance. Under the direction of Dr. Robert Walker, DAFM's key research goals are to characterize and identify ways to reduce microbial hazards associated with all phases of animal food production and to address the effects of therapeutic and non-therapeutic antimicrobials used in food-producing animals on commensal bacteria and foodborne bacterial pathogens.

Antimicrobial Resistance

To achieve these public health goals, DAFM collaborates on and has initiated a number of research studies, both internally- and externally-funded, aimed at developing approaches to support the safe use of antimicrobial drugs in food animals, including aquatic species. However, the bulk of DAFM's research focuses on studies aimed at detecting and avoiding development of antibiotic resistant bacteria in the human food chain. A listing of some of DAFM's studies on antimicrobial resistance follows.

Improving Reliability of Microbiological Tests

Currently, many microbiological tests suffer from poor reproducibility, poor comparability, and lack of agreement among microbiologists as to which tests are reliable and should be used by all investigators. Recognizing these shortcomings, Dr. Walker and his team recently performed comparison studies of two widely-used microbiological testing methods for *Campylobacter*—the concentration gradient (Etest) and agar dilution method tests. The DAFM team coordinated experiments and compared results from various investigators around the U.S. and showed that the agar dilution test was uniquely reliable for quantifying antimicrobial susceptibility in *Campylobacter*. Dr. Walker presented these results at a recent NCCLS-VAST subcommittee meeting and the group agreed that the agar dilution method should be the standard for *Campylobacter* in vitro antimicrobial susceptibility testing. Moreover, the group agreed upon quality control (QC) limits for various antibiotics for the agar dilution method for testing *Campylobacter*.

PulseNet: Genetic Fingerprinting of Antibiotic-Resistant Bacteria

Another of DAFM's projects, PulseNet, has already been highly successful in characterizing and reducing salmonellosis outbreaks. PulseNet is a program designed to provide DNA fingerprints of foodborne bacterial pathogens and store them for future reference in outbreaks. To give an example of PulseNet in action, in the fall of 1999, 30 individuals in Canada developed *Salmonella infantis*. All those affected were dog owners and many had recently given their dogs pig ear dog treats. Shortly thereafter, the FDA issued a nationwide public health warning on salmonellosis related to contact with these dog treats. PulseNet scientist Dr. Shaohua Zhao isolated and serotyped *Salmonella* bacteria from various brands of dog treats. She also established PFGE profiles of the *Salmonella* serotypes and later determined the antibiotic susceptibility of the various serotypes found in the dog treats. Following Dr. Zhao's work, a nationwide FDA survey (involving 16 FDA district offices and 7 regional labs) showed that 49% of dog treats tested carried

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Salmonella, and that 36% of serotypes were resistant to one or more antimicrobials with 13% being resistant to 4 or more antimicrobials. In a collaboration with the National Antimicrobial Resistance Monitoring System (NARMS), DAFM researchers shared PulseNet data to determine the association between animal and human *Salmonella* isolates and to assess mechanisms of antibiotic gene transfer. These same highly successful DNA fingerprinting techniques are being used to examine the possible presence of fluoroquinolone-resistant *Campylobacter* in retail meats (chicken, turkey, beef, and pork).

AQUACULTURE

Americans are increasingly health conscious and are more aware of the beneficial effects from eating fish. Thus, the supply and consumption of fish within the U.S. has been steadily increasing over the past 20 years. To meet this demand, aquaculture (or the farming of aquatic organisms including fish, mollusks, crustaceans and aquatic plants) is a rapidly growing industry.

As the number of aquaculture facilities increases, so does the need to develop safe and effective drugs for treating fish diseases. It is critical to understand the effect these treatments might have on fish (and consumers), non-target organisms and on the aquatic environment. As a result, CVM has greatly expanded its commitment to aquaculture research. In January 1999, Dr. Renate Reimschuessel joined OR to develop a research program in aquaculture. Dr. Reimschuessel's key achievements have largely focused on optimizing OR's aquaculture facility such that it can support diverse studies in multiple fish species.

OR's research objectives for aquaculture are to provide data to assist the FDA in assuring that fish derived from aquaculture are safe for human consumption. Species for study include tilapia (*Oreochromis sp.),* rainbow trout *(Oncorhynchus mykiss)*, Atlantic salmon (*Salmo salar*), channel catfish (*Lctalurus punctatus*) large mouth bass *(Micropterus salmoides*), toadfish (*Opsanus tau*), and goldfish (*Carassius auratus*)—with goldfish being an established model for fish infections. All species, except goldfish, are currently raised for food purposes. There also has been a large effort to develop a rationale for crop grouping (grouping species for drug approvals based on similarities in anatomy, physiology, and drug metabolism).

Since much of the U.S. fish supply is currently from countries where aquaculture drug usage is widespread, it is also critical to conduct drug targeting studies and surveys of aquatic food species being marketed in the USA. In addition, of increasing importance, are studies designed to understand the development and transmission of antimicrobial resistance in both pathogenic and environmental microbes. Understanding those mechanisms will help in designing treatment strategies that minimize the development of resistant pathogens.

STEC AND SALMONELLA ANTIBIOTIC RESISTANCE IN CATTLE

DAFM is collaborating with Dr. David Acheson at New England Medical Center to examine Shigatoxin producing E. coli (STEC), e.g., E. coli 0157:H7, and *Salmonella* in cattle. These studies will determine the epidemiology of antimicrobial resistance phenotypically and genotypically in *Salmonella* and STEC as the organisms move longitudinally from feed into animals.

PREVENTION OF WATERBORNE E. COLI TRANSMISSION

DAFM collaborates with Dr. Charles Kaspar at the University of Wisconsin-Madison on a study examining the waterborne transmission of Escherichia coli 0157:H7 in cattle. Molecular subtyping of Escherichia coli isolates is also being done to assess possible development of new E. coli strains. Finally, this information will be used in developing prevention scheme strategies for on-farm control of E. coli transmission.

SURVEILLANCE

DAFM also performs surveillance studies of retail products for foodborne bacterial pathogens to assess trends of antibiotic resistance in animal foods for humans. The above represent just a few of the ongoing highly-successful research studies being conducted by DAFM scientists. These studies are achieving the President's Food Safety Initiative (FSI) goal of helping to reduce the incidence of foodborne disease to the greatest extent possible. □

CVM's LEVERAGING ACTIVITIES

FDA is exploring new opportunities to leverage its own assets by working with other organizations in order to carry out its public health mission effectively in the 21st Century. Leveraging is the creation of relationships and/or formal agreements with others outside the FDA that will ultimately enhance FDA's ability to meet its public health mission. These collaborations are intended to have a larger net public health benefit to the American public than would be possible if FDA worked alone. The Agency is currently working closely with a diverse set of partners—including public health organizations, scientific experts, other Federal regulators, States, industry and consumers—to expand these benefits.

CVM has two strategic goals for carrying out leveraging efforts. The first goal is ***to increase the availability and diversity of safe and effective animal drugs and feeds.***

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FDA's Animal Drugs and Feeds Program informs and assists product sponsors throughout the approval process starting with the pre-submission conference. The focus is to inform and assist firms in complying with the new legislation and streamline the product review process through phased review. Instead of waiting until all stages of product development are completed before contacting FDA, phased review helps industry stay on course through the drug development process by communicating requirements (or standards or criteria) for approval at each stage of development.

Staff College programs have been developed in FDA as a means of developing intellectual capital. The addition of a CVM Staff College will allow CVM to increase and maintain the scientific expertise in the Center, especially as it relates to animal science and veterinary medicine issues. The Staff College will use dollars to outsource the planning and implementation of training programs tailored to the needs of in-house scientists.

Collaboration with other agencies such as the Centers for Disease Control and Prevention (CDC) and the U.S. Department of Agriculture (USDA) is accomplished through interagency agreements. FDA also funds extramural research via contract and cooperative agreements and through collaboration with the University of Maryland known as the Joint Institute for Food Safety and Applied Nutrition (JIFSAN).

CVM's second strategic goal is to ***reduce the risks associated with marketed animal products.***

In order to assure that foods from animals are safe for human consumption, FDA works with other government agencies, State and local governments, and the private sector to take action to prevent or minimize potential public health hazards through development of early warning systems, investigations, risk assessment, scientific research, educational initiatives and regulatory action.

CVM partners with other Federal and State agencies, our stakeholders, and regulated industry to develop and sponsor workshops, symposia, and publications with a focus on prevention in order to assure the public that accurate information is disseminated and that marketed animal drugs and feeds are safe and effective.

CVM is making a strong effort to educate its partners in industry by publishing and disseminating guidance, training initiatives in targeted high-risk compliance areas, and in working more closely with industry to resolve problems.

FDA is also involved in international harmonization activities that will remove trade barriers while ensuring the American public that imported products meet FDA's standards related to safety and efficacy. Part of the harmonization effort includes the development of Mutual Recognition Agreements (MRA's) that will address international equivalency issues. FDA must be able to assure the public that the processes used in other countries are as good as the processes in this country and the resulting products are safe for the intended use. Harmonization activities have been initiated with the European Union and Japan. The assessment of Member State regulatory systems is essential to the harmonization process.

By choosing to work with other organizations that share our public health and safety goals, FDA can significantly amplify its public health impact, leverage the intellectual capital of others, and make wise use of its resources. FDA has been quite successful with its past collaborations and the agency intends to expand and build upon this solid foundation in developing new partnerships. Successful leveraging provides benefits and incentives to all participants, including consumers, industry, academia, health providers, and other government agencies. In addition, greater benefits are produced by sharing talent and material resources and achieving results through synergism. For further information about leveraging, please visit the web site at *http://www.fda.gov/oc/leveraging/default.htm*. The following article relates to international collaboration between the U.S. and the European Union. □

FDA'S PHARMACEUTICAL GMP PROGRAMS ASSESSED BY EU

by Merton V. Smith, Ph.D., J.D.

Introduction

Earlier this year the tables were turned on FDA. The Agency was on the receiving end of something that it usually only gives out—an audit of its quality assurance programs and procedures. For three weeks in March, representatives of the European Commission visited FDA at its Rockville headquarters offices and its Philadelphia and Kansas City field offices to observe how the Agency sets standards and monitors and enforces the pharmaceutical industry's compliance with Good Manufacturing Practices (GMPs).

This audit was undertaken as part of the implementation of an international agreement between the U.S. and the European Union (EU) entitled "Annex on Pharmaceutical Good Manufacturing Practices of the Mutual Recognition Agreement" (MRA). This agreement was signed in 1998 and is now in the third year of its transition period. The U.S./EU MRA is one of the most significant international agreements that FDA has entered into—both in terms of extent of the commitments involved and the level of

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resources that will be necessary to complete the activities described in the agreement.

International Cooperation—Leveraging FDA's Resources

These kinds of audit activities by foreign governments have not been limited just to FDA's regulatory systems covering GMPs for pharmaceuticals shipped to Europe. Similar audits have been taking place with regard to seafood products that are exported to Canada and EU Member States, dairy and egg products that are exported to EU Member States, and medical devices that are exported to EU Member States. In addition to foreign government interest in FDA's regulatory programs, FDA experts also have begun examining and assessing the programs of countries that export foods, drugs, biologics, and devices to the United States.

To better appreciate why FDA and its foreign government counterparts are taking such a keen interest in one another's regulatory systems, it is useful to understand some of the legal and policy reasons that underlie these initiatives.

The primary driving force behind these cooperative activities has been the enormous increase in international trade and the need of governments to provide more assurance of the safety of imported products. The global market place for foods, drugs, biologics, and medical devices is not only a reality, but also a reality that is outpacing even our highest estimates. Because safety of imports cannot be achieved solely by surveillance at the borders, the situation demands increased cooperation and collaboration between FDA and its regulatory partners around the world.

Many of FDA's international cooperative relationships with foreign governments have been formalized as international agreements. FDA believes that these cooperative activities, if properly structured, can be very effective in permitting it to have a high level of confidence in the accuracy and validity of inspectional and other regulatory information that is provided by foreign governments.

Such agreements are not a new idea for FDA. For more than fifty years the agency has participated in a number of regulatory cooperation agreements with other countries; and, at present, has more than fifty agreements with its counterparts in other countries. They have a variety of names, including "Memoranda of Understanding," "Memoranda of Cooperation," and "Cooperative Arrangements."

Authority for FDA to enter into these kinds of agreements comes from the Federal Food, Drug, and Cosmetic Act; particularly from the 1997 FDA Modernization Act amendments that require the agency to meet with representatives of other countries "to discuss methods and approaches to reduce the burden of regulation and harmonize regulatory requirements if the Secretary determines that such harmonization continues consumer protection consistent with the purposes of the Act." Furthermore, the 1997 Act requires FDA "to move toward the acceptance of mutual recognition agreements relating to the regulation of drugs, biological products, devices, foods, food additives, and color additives, and the regulation of good manufacturing practices, between the EU and the United States" and "to participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements."

FDAMA also required that FDA develop a plan that establishes a framework for achieving mutual recognition of good manufacturing practices inspections. In May of 1998, FDA made its plan public. This plan specified that

> ". . . before accepting the procedures and activities, including enforcement methods, of foreign governments as equivalent to its own, FDA will seek assurance that such activities provide the same level of product quality, safety and efficacy that is provided under the FFDCA; the Fair Packaging and Labeling Act; the Public Health Service Act; and any other relevant law of the United States. FDA may find it necessary to confirm by on-site review or other appropriate means that the foreign government agency has the necessary authorities, product standards, capabilities, and infrastructure to successfully achieve the proposed terms of the MOU, and, therefore, that a determination of equivalence can be made.

This plan is also in keeping with two World Trade Organization (WTO) Agreements that the U.S. Government has signed—the Agreement on the Application of Sanitary and Phytosanitary (SPS) Measures and the Agreement on Technical Barriers to Trade (TBT).

The SPS and TBT agreements encourage harmonization of regulatory standards as well as recognition of the results of conformity assessment procedures by other WTO member countries, even when such procedures are different, provided that they are satisfied that those procedures are equivalent. Equivalent regulatory systems need not be identical. Under the concept of equivalence, the regulatory system utilized by the exporting country may differ from that applied domestically by an importing country so long as the exporting country's regulatory system achieves the importing country's level of public health protection. Furthermore, under the SPS and TBT agreements, the burden of demonstrating that equivalence exists rests with the exporting country. The SPS and TBT agreements specify that the exporting country allow "reasonable access" to the importing country to inspect or carry out other procedures for evaluating equivalence. If the exporting country can demonstrate equivalence, the importing country "shall accept" the exporting

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country's regulatory system as equivalent. The SPS and TBT agreements also encourage member countries to enter into negotiations with the aim of achieving bilateral and multilateral agreements for the mutual recognition of the results of conformity assessment procedures. Under these agreements, every finding of regulatory system equivalence between member countries is not required to result in a bilateral or multilateral agreement; but these agreements do require that member countries consult, if requested, with the potential goal of a mutual recognition agreement as a possibility.

In addition to the U.S./EU MRA, there are other international agreements that will play an important role in FDA's regulatory programs. For example, the seafood Hazard Analysis Critical Control Points (HACCP) regulation that took effect in December 1997 provides an advantage to importers who facilitate the entry of products from countries that have agreements with FDA in the area of seafood safety and quality control. Specifically, under FDA's HACCP regulation importers representing manufacturers located in countries that have entered into an international agreement with FDA covering HACCP equivalency are not required to provide FDA with verification that the manufacturers are using their HACCP plans. This regulatory provision has already generated many requests from foreign countries to enter into such agreements with FDA. FDA's Office of Seafood indicates that there are already about 40 countries that are interested in HACCP equivalency agreements and has estimated that there are potentially up to 70 countries that may seek these agreements.

FDA knows that significant "up-front" costs will be required to develop the kind of international agreements that will provide FDA with the confidence that it needs to utilize information received by its regulatory counterparts around the world. These up-front costs include the resources needed to assess foreign regulatory systems but also the resources needed to prepare for and host foreign officials who are auditing FDA's programs. FDA believes that these costs are well spent because well-crafted agreements can complement the agency's important efforts in import surveillance and foreign inspection work for the areas covered. Such cooperative agreements can also permit the agency to redirect existing resources to higher priority areas.

Pharmaceutical GMP Annex of the U.S./EU MRA

The stated purpose of the Pharmaceutical GMP Annex is to "govern the exchange . . . and normal endorsement . . . of official Good Manufacturing Practices (GMPs) inspection reports after a transition period aimed at determination of the equivalence of the regulatory systems of the Parties, ..." To this end, the annex describes activities and processes that will occur during two distinct periods, the transition period (when equivalence assessments will be made) and the operational period (when pharmaceutical GMP inspection reports provided by equivalent exporting authorities will be normally endorsed by equivalent importing authorities). The products covered by the MRA are medicinal products for human or animal use, including intermediates and starting materials (under EU law) and drugs for human or animal use, biological products for human use, and active pharmaceutical ingredients (under U.S. law). Products (for example, dietary supplements) which otherwise fall into the above definitions but are not regulated by the authorities of both parties are not included. The following products are also not included: human blood, human plasma, human tissues and organs, and veterinary immunologicals. Other products are excluded during the transition period (but may be reconsidered for inclusion at the end of the transition period): human plasma derivatives, investigational medicinal products/new drugs, human radiopharmaceuticals and medical gases.

The MRA also describes the criteria that the regulatory authorities of the importing countries will apply to determine the equivalence of the regulatory systems of the exporting countries. Such equivalence determinations will include an assessment of the legal/regulatory authority, structure, and procedures; mechanisms to assure appropriate professional standards and avoidance of conflicts of interests; administration of regulatory authority; conduct of inspections; execution of regulatory enforcement actions to achieve corrections, actions intended to prevent future violations, and actions to remove violative products from the market; effective use of surveillance systems; and ability to verify the authenticity and completeness of critical data supporting an application such as that relating to scale-up capability and other essential information.

EU Audits Under the Pharmaceutical GMP Annex of the MRA

On March 7, Inspector Muireann Lydon of the Irish Medicines Board and Inspector Sabine Atzor of the German Department of Medicinal Products on behalf of the European Commission began their audit of FDA by being briefed by representatives of CDER, CBER, CVM, ORA, and OC at the Parklawn Building. The headquarters agenda included more detailed descriptions by program managers at MPN I, MPN II, Woodmont, Piccard, and Crabbs Branch locations covering FDA's quality management system, program guidance for both pre-approval inspections and post-approval inspections, emergencies workplan, field laboratories, recalls, regulatory policy, legal actions, imports, investigator training, quality reports, product surveillance, manufacturing site registration, product listing, export certificates, GMP case review and program support, and, for biologics, lot

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release and Team Biologics inspection planning, conducting, reporting, and case processing.

The auditors then moved on to Philadelphia and Kansas City where they were joined by three EU inspectors: Elena Casaus Lara and Christina Gomez, both of the Spanish Ministry of Health, Division of Medicinal Safety, and Jorg Neuhaus of the German Department of Medicinal Products. In these locations they examined FDA's field programs and activities in the Central Region Regional Office, the Philadelphia District Office, and the Kansas City District Office. The EU auditors also accompanied FDA investigators on two evaluation inspections of pharmaceutical manufacturers: Over-the-Counter liquid and tableted products for human use produced at a Johnson & Johnson Merck Consumer Pharmaceuticals Co. manufacturing site in Lancaster, Pennsylvania and sterile hospital products produced at an Abbott Laboratories site in McPherson, Kansas. These field activities concluded on March 30. While FDA will not know how it performed in the eyes of the EU until a final assessment report is issued, those FDAers that participated believed that the Headquarters, District Offices, and Regional Office were well-prepared and did an excellent job in describing FDA's pharmaceutical GMP-related regulatory programs and how they operate. It was also believed that FDA inspection teams performed well and did a good job in representing the field and the agency. The FDA teams followed their planned inspectional outline closely and were open and communicative both with the firms and with the EU auditors. As appropriate for an audit process, the EU representatives did not participate in the inspectional process other than to ask questions for clarification or to look at documentation.

Final Thoughts

Some have suggested that international equivalence assessments and harmonization efforts will ultimately lower the bar for safety standards of foods, drugs, and devices. On the contrary, FDA believes that focussed, open, and frank discussion by experienced experts about how best to structure regulatory controls to protect the public health will result in quite the opposite effect—that is, it will raise the safety bar. Indeed, one of the greatest benefits for FDA in implementing equivalence-based international agreements such as the U.S./EU MRA is the open and frank discussion between public health regulatory partners about how they both can more effectively perform their jobs. Experience has shown FDA that these kinds of discussions provide a cross-fertilization of ideas that raise regulatory standards and procedures on both sides.

FDA is pleased that the EU auditors are looking closely at the U.S. regulatory system and are attempting to identify areas where the Agency can improve. FDA values the fact that the Commission has chosen experienced and competent inspectors from well-respected EU Member States to perform the audits of FDA's system. These inspectors and others working for the European Commission also have been examining how the EU Member State regulatory systems are performing to assure that manufacturers operating in those countries meet GMP requirements. The Commission has been looking at the regulatory systems and controls of some of its other major trading partners as well, including Canada, Japan, Australia, and New Zealand.

These pharmaceutical GMP assessments will continue with future visits by EU auditors. Of course, FDA will be very interested in the final evaluations when these EU audits are concluded. FDA plans to begin its on-site assessments of the EU and EU Member State pharmaceutical GMP regulatory systems as soon as it further evaluates the documentation that has been received from the EU that describes these systems. Initial on-site audits of the EU and its Member States will probably begin this summer.

Dr. Smith is Associate Director, International Agreements, Office of International Programs in the Office of the Deputy Commissioner for International and Constituent Relations. During February-March 2001, Dr. Smith was on detail to the Office of the Director, CVM where he was responsible for the Center's international programs. □

CVM SCIENTISTS WIN AWARDS

At the 2001 FDA Scientific Achievement Awards Ceremony, held on February 16, 2001, the following CVM scientists were recognized:

- Michaela G. Alewynse, Ph.D.—**"Excellence in Review Science"** for excellence in the scientific review of the utility and safety of fermentation products and other microbial derivatives used in animal feed and feed ingredients.
- Patrick F. McDermott, Ph.D.; Renate Reimschuessel, V.M.D., Ph.D.; Shabbir Simjee, Ph.D.; David D. Wagner, Ph.D.; Robert D. Walker, Ph.D.; David G. White, Ph.D.; and Shaohua Zhao, D.V.M.—**"Excellence in Laboratory Science"** for exemplary performance in addressing the microbiological safety of animal derived food.
- Jeffrey M. Gilbert, Ph.D., CVM; Roger A. Jones, Ph.D., CVM; Ashraf A. Khan, Ph.D., CVM; Saeed Khan, Ph.D., NCTR; Mohammed S. Nawaz, Ph.D., NCTR; and Robert D. Walker, Ph.D., CVM—Nominated for the Outstanding Intercenter Scientific Collaboration Award, **"CVM/NCTR Antimicrobial Resistance Collaborative Research Team"** for outstanding contribution to the understanding of emergence and dissemination of antimicrobial resistance in environmental settings and for the detection thereof in competitive exclusion cultures.

The Center for Veterinary Medicine is proud of these accomplishments and congratulates all FDA award winners. □

FDA/CVM 1999 ADVERSE DRUG EVENT REPORTS – A DESCRIPTIVE OVERVIEW

by Neal Bataller, ME, D.V.M.

I. Introduction

This article presents a descriptive overview of the 9,731 post-market adverse drug event (**ADE**) reports received by the U.S. Food and Drug Administration, Center for Veterinary Medicine (**FDA/CVM**) during calendar year 1999. An ADE report consists of either an undesired side effect, or the lack of a desired effect associated with drugs administered to animals. Reports may also involve product defects and potential harm posed to persons administering or using animal drugs.

In previous years, a summary of these ADE reports was included as an insert in the *FDA Veterinarian*. This summary was not included in the newsletter this year because of its length. However, copies of the 1999 Veterinary Adverse Drug Experience Summary may be obtained from CVM's Internet Home Page (http://www.fda.gov/cvm) or by calling or writing the *FDA Veterinarian*.

The primary purpose for maintaining the FDA/CVM database is for providing an early warning or signaling system for adverse effects not detected during premarket testing of FDA-approved animal drugs and for monitoring the performance of drugs not approved for use in animals. The FDA/CVM ADE reporting system depends upon the detection of an adverse clinical event by veterinarians and animal owners, the attribution of the clinical event to the use of a particular drug ("suspect" drug), and the reporting of the ADE either to the manufacturer of the suspected drug or directly to FDA. Data from these ADE reports are reviewed, coded and entered into the computerized FDA/CVM ADE database.

The reporting of ADEs by veterinarians and animal owners is voluntary. They may send their reports directly to the FDA/CVM ("Direct" reports), to the drug manufacturer ("Manufacturer" reports), or both. The drug manufacturers of FDA-approved animal drugs are required by law and regulation to submit to the FDA post-market ADE reports received by any means from veterinarians and animal owners.

It is important to remember certain caveats when using data from the FDA/CVM ADE database:

1. For any given ADE report, there is no certainty that the suspect drug caused the ADE. This is because veterinarians and animal owners are encouraged to report all suspected ADEs, not just those that are already known to be caused by the drug. The adverse event may have been related primarily to an underlying disease for which the drug was given, to other concomitant drugs, or may have occurred by chance at the same time the suspect drug was administered.
2. Accumulated ADE reports should not be used to calculate incidence rates or estimates of drug risk.
3. Many factors affect the volume of reports received for any one drug product. Factors might include (1) the nature of the drugs; (2) the diseases being treated; (3) the type and health of the patient involved; (4) the motivations and expectations of consumers; (5) the extent of product marketing; and (6) the vigilance of the drug company in receiving and submitting reports of adverse drug experiences. In consideration of these many factors, the summarized information should NOT be used to make product comparisons or to commercially promote certain products.

In this article, various kinds of data and information are presented for the ADE reports computerized into the FDA/CVM ADE database during the calendar year 1999. Due to rounding, the percentages in tables may not total to 100 percent.

II. Report Submission Information

Table 1 shows the number of reports received for the last eight full calendar years. The numbers only include original reports involving animal injury and product ineffectiveness; follow-up reports are not included. Product defects are additionally included for 1999 but are not included in the figures for previous years. In general, the annual number of reports has increased in recent years, although much of the increase in the latter years is attributable to a few newly approved animal drugs. Reporting levels for the last two years are similar.

TABLE 1.
ADE Reports by Year

Year	Number
1992	1,011
1993	1,250
1994	1,746
1995	3,193
1996	3,112
1997	4,738
1998	9,385
1999	9,731

While ADE reports are submitted to CVM from a variety of sources, the sponsors of FDA-approved animal drugs submit the bulk of reports (Table 2). As mentioned above, drug sponsors are required by law and regulation to submit all reports involving animal injury, product ineffectiveness, and product defects. Drug manufacturers of human drugs and unapproved animal drugs are not required to submit any ADE reports to CVM, so very few ADE reports are submitted to CVM for these types of drug products.

The USP Practitioner Reporting Network is a "third-party", independent reporting service. Only selected USP ADE reports are entered into the FDA/CVM ADE database. Selected

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TABLE 2.
1999 ADE Reports
Ranked by Source (n=9,731)

Source	*Number*	*%*
Drug Company	9,627	98.9
USP Practitioner Reporting Network	59	0.6
Mail, Direct to FDA	43	0.4
Telephone, Direct to FDA	2	<0.1

TABLE 3.
1999 ADE Reports Ranked by Top-10 Species, Plus Average Number of Animals Adversely Affected per Report (n=9,731)

Species	*Number*	*%*	*Avg #/Rpt*
Dog	6,502	66.8	1.1
Cat	865	8.9	1.5
Cattle	728	7.5	98.9
Horse	412	4.2	1.6
Human	293	3.0	0.4
Pig	55	0.6	1,198.4
Goat	16	0.2	6.8
Sheep	9	<0.1	7.0
Rabbit	7	<0.1	1.4
Deer	5	<0.1	6.8

TABLE 4.
1999 "Possible" ADE Reports
Ranked by Top-10 Classes
of Suspect Drugs (n=7,619)

Class	*Number*	*%*
Anti-inflammatory/ Analgesic, Nonsteroidal	3,116	40.9
Antinematodal	815	10.7
Heartworm Treatment/ Prevention	716	9.4
CNS, General	680	8.9
Antimicrobials, Penicillins	258	3.4
Anesthetics, General	248	3.3
Antimicrobials, Fluoroquinolones	194	2.5
CNS Sedatives/Hypnotics	183	2.4
Anti-ectoparasites, Systemic	145	1.9
CNS, Tranquilizers	137	1.8

reports include reports involving unapproved animal drugs and human drugs, and where the identity of the reporter is withheld from the sponsor. For the remaining USP reports, the sponsor is expected to investigate the adverse event and officially submit their findings directly to CVM.

III. Animal Zoographic Information

Table 3 lists the species that are most represented in ADE reports. The majority of reports involve companion animals and cattle. Few reports are received that involve poultry; chicken and turkeys did not make the 1999 Top-10 list. The average

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TABLE 5.
1999 "Possible" ADE Reports
Ranked by Top-10 Active Ingredients
of Suspect Drugs (n=7,619)

Active Ingredient(s)	*Number*	*%*
Carprofen	2,541	33.4
Seligiline	675	8.9
Etodolac	492	6.5
Moxidectin	432	5.7
Milbemycin, Lufenuron	183	2.4
Selamectin	178	2.3
Doramectin	166	2.2
Medetomidine	163	2.1
Amoxicillin	150	2.0
Enrofloxacin	144	1.9

TABLE 6.
1999 "Possible" ADE Reports
Ranked by Top-10 Tradenames of
Suspect Products (n=7,619)

Tradename	*Number*	*%*
Rimadyl®	2,541	33.4
Anipryl®	675	8.9
Etogesic™	492	6.5
Quest™	312	4.1
Sentinel™	183	2.4
Revolution™	178	2.3
Domitor®	163	2.1
Immiticide®	150	2.0
Posilac®	123	1.6
Cydectin®	118	1.5

TABLE 7.
1999 "Possible" ADE Reports Ranked by Top-10 Routes of Drug Administration (n=7,619)

Route	*Number*	*%*
Oral	4,895	64.2
Not Applied, Product Defect	813	10.7
Intramuscular	555	7.3
Subcutaneous	364	4.8
Topical	358	4.7
Intravenous	203	2.7
Unknown Route	160	2.1
Intramammary	85	1.1
Otic	84	1.1
Medicated Feed	39	0.5

TABLE 8.
1999 "Possible" ADE Reports Ranked by Top-10 Adverse Clinical Manifestations (n=7,619)

Adverse Effect	*Number*	*%*
Vomiting	1,146	15.0
Anorexia	944	12.4
Depression/Lethargy	910	11.9
Product Ineffectiveness	692	9.1
Increased SGPT/ALT	684	9.0
Increased Alkaline Phosphatase	683	9.0
Death	587	7.7
Diarrhea	485	6.4
Ataxia	382	5.0
Increased Total Bilirubin	370	4.9

number of animals adversely affected in each report is more reflective of the animal management and health care associated with each species, and with the type of complaint.

IV. Suspect Drug Information

The remaining tables (4 through 8) in this article only involve reports that the Center has determined to be at least "possibly" drug-related. A number of different factors are considered in determining this classification. Tables 4 through 6 describe the drugs involved in these reports with the data organized by (1) general drug class; (2) active ingredient(s); and (3) product tradename.

V. Drug Usage Information

Table 7 lists the route of drug administration most commonly represented in ADE reports. Note that the "oral" category generally represents tablets, capsules, powders and pastes while the medicated feed category involves the consumption of animal feeds containing drugs.

VI. Adverse Event Information

Table 8 lists the most common complaints contained in ADE reports considered as at least "possibly" drug-related. Again, care should be taken in interpreting this ranking since many factors affect whether a veterinarian or animal owner is motivated to actually report an adverse drug experience. The seriousness of an adverse event may affect the likelihood of reporting regardless of whether other non-drug-related factors could also have accounted for the adverse event.

Dr. Bataller is a Biologist in CVM's Division of Surveillance.

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IRRADIATION OF ANIMAL FEED

On April 10, 2001, FDA approved a food additive petition for an irradiation process that can be used on all animal feed and feed ingredients, including pet treats, to reduce the risk of Salmonella contamination. Salmonella is a foodborne pathogen that may be present in these feeds.

Irradiation is a process whereby products are exposed to sources of ionizing radiation which cause chemical changes similar to other conventional cooking or preservation methods. It has been approved for use on a variety of human foods. Extending this process to animal feed and feed ingredients will not only increase the safety of the feed for the animals consuming it, but to people who handle animal feed and feed ingredients. Irradiation is a useful tool for reducing disease risk.

Irradiation treatment compliments, but does not replace, the need for proper food handling practices in the production, processing, and handling of animal feed and pet foods including treats. Pet owners still need to practice safe food handling practices after handling pet treats, including washing hands thoroughly in warm water and soap after any contact.

The petition was filed by Sterigenics International, of Fremont, California.

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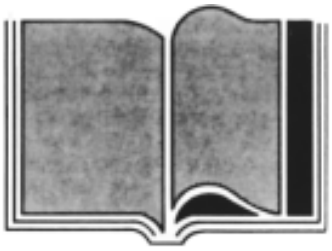
PUBLICATIONS



FDA Veterinarian – Index Available

A topical index for the 2000 *FDA Veterinarian* is now available on the CVM Internet Home Page at *http://www.fda.gov/cvm/index/fdavet/2000/00index.pdf.* Readers who wish to obtain a paper copy of the Index may call or write the *FDA Veterinarian*.

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PROCEDURAL CHANGES TO THE ANNUAL REGISTRATION OF DRUG ESTABLISHMENTS

FDA's Center for Drug Evaluation and Research (CDER) has implemented a new system for the 2001 annual registration of drug establishments. This includes veterinary drug establishments and licensed medicated feed mills. CDER will no longer issue to registered owners and operators of drug establishments the computer generated printout of the Form FDA 2656e (Annual Registration of Drug Establishment). The new renewal procedure will require registered establishments to obtain, complete, and submit a Form FDA 2656 (Registration of Drug Establishment) using one of the following formats:

- **IF THERE IS NO CHANGE SINCE PREVIOUS REGISTRATION** – the firm is to fill out the form with only the labeler code (not required for medicated feed mills), registration number, reporting firm name, and signature, title, and date. The *Reason for Submission* box should be filled out to read "Annual-No Change".
- **IF THERE IS A CHANGE(S) SINCE PREVIOUS REGISTRATION** – the form is to be filled out with the labeler code (not required for medicated feed mills), registration number, reporting firm name, and signature, title, and date, and any applicable sections where a change has occurred. The *Reason for Submission* box should be filled out to read "Annual".

These directions are also available on the CDER information line at (301) 594-1086. This information line also instructs establishments on how to obtain copies of the Form FDA 2656. The Form also may be found on the Program Support Center Home Page at: *http://forms.psc.gov/forms/FDA/fda2656.pdf*

CDER recommends that the establishments follow the registration schedule as outlined in 21 CFR 207.21(a) (*http://www.access.gpo.gov/nara/cfr/waisidx_00/21cfr207_00.html).* □

RUMINANT FEED (BSE) ENFORCEMENT ACTIVITIES

This is more recent information on ruminant feed (BSE) enforcement activities. FDA previously provided information on this issue in a January 10, 2001, CVM UPDATE (*http://www.fda.gov/cvm/index/updates/bseup.htm*). Active monitoring by the U.S. Department of Agriculture (USDA) has found *no cases* of bovine spongiform encephalopathy (BSE) in U.S. cattle.

To prevent the establishment and amplification of BSE through feed in the United States, FDA implemented a final rule that prohibits the use of most mammalian protein in feeds for ruminant animals. This rule, Title 21 Part 589.2000 of the *Code of Federal Regulations*, became effective on August 4, 1997.

FDA's enforcement plan for the ruminant feed rule includes education as well as inspections with FDA taking compliance actions for egregious actions or repeated non-compliance. As part of the enforcement plan, an assignment was issued to all FDA District Offices in 1998 to conduct inspections of 100% of all renderers and feed mills and some ruminant feeders to determine compliance. FDA's Center for Veterinary Medicine (CVM) has assembled data from the inspections conducted as of February 27, 2001.

As of that date, there had been a total of 10,240 inspections of 10,065 firms. The majority of these inspections (around 80%) were conducted by State officials and the remainder by FDA. Various segments of the feed industry had different levels of compliance.

FOR RENDERERS, who are the first to handle rendered protein, and who send materials to feed mills and other ruminant feeders:

- Estimated number of rendering firms in the U.S. -- 260
- Number of firms inspected -- 227
- Number of firms handling material prohibited for use in ruminant feed -- 177 (77% of those firms inspected).

  Of the 177 renderers handling prohibited material:
  - Those whose products were labeled with the required caution statement -- 96%
  - Had a system to prevent commingling -- 86%
  - Followed recordkeeping regulations -- 97%

FOR FDA LICENSED FEED MILLS:

- Estimated number of licensed feed mills -- 1,240
- Number of licensed feed mills inspected -- 1,069
- Number of licensed feed mills handling material prohibited for use in ruminant feed -- 397 (37% of those licensed feed mills inspected).

  Of the 397 handling prohibited material:
  - Those whose products were labeled with the required caution statement -- 85%
  - Had a system to prevent commingling -- 87%
  - Followed recordkeeping regulations -- 99%

FOR NON-FDA LICENSED FEED MILLS:

- Estimated number of non-FDA licensed feed mills -- 6,000-8,000 (FDA does not know the total number since they are not required by the Agency to be licensed).
- Number of non-FDA licensed feed mills inspected -- 5,064

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- Number of non-FDA licensed feed mills handling material prohibited for use in ruminant feed -- 1,829 (36% of those non-FDA licensed feed mills inspected).

  Of the 1,829 handling prohibited material:

  – Those whose products were labeled with the required caution statement -- 67%

  – Had a system to prevent commingling -- 82%

  – Followed recordkeeping regulations -- greater than 99%

The rule requiring a firm to have a system to prevent commingling is triggered when the firm is manufacturing products that contain prohibited material in the same facility it is manufacturing products that do not contain prohibited material.

In January 2001, FDA field offices were issued an assignment to re-inspect 834 firms that were not in full compliance with the rule. As FDA anticipated, because many of these firms had committed to implementing the regulation, there have been higher levels of compliance after completion of follow-up inspections. Of the 157 re-inspections of renderers, feed mills, and other facilities that had been conducted by February 27, only one firm, a rendering firm, continued to be out of compliance. FDA continues to conduct these re-inspections, and FDA and State feed control officials continue conducting initial inspections.

A spreadsheet containing information about inspections conducted under the FDA's ruminant feed (BSE) rule has been posted on FDA/Center for Veterinary Medicine's (CVM's) Home Page at: *http://www.fda.gov/cvm/efoi/efoi.html*.

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REGULATORY ACTIVITIES

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

- Peter Linssen, Owner, Michigana Farms, Ltd., Scotts, MI
- Roger Masselink, Owner, Roger Masselink Dairy, Middleville, MI
- Peter deVries, General Manager, Royal Farms Dairy, LLC, Garden City, KS
- Gregg Jeffers, Owner, Gregg Jeffers Farm, Poplar Grove, IL
- George Ainger, Co-Owner, Ainger Farm, Harvard, IL
- Jay N. Martin, Owner, Jay N. Martin AKA Horizon Dairy, Clyde, NY
- David C. Footit, Owner, D & K Farm, Middlefield, CT
- Rick L. Gorzeman, Cornerstone Dairy, Tipton, CA
- Michael Hummermeier, Owner, Hummermeier Farm, Pearl City, IL
- Craig Hessenius, Craig Hessenius Farm, Freeport, IL
- Daniel E., Robert F., Thomas A., and John M. Curtin, Partners, Curtin Dairy, LP, Cassville, NY
- George and Gloria Soares, Log Haven Dairy, Hanford, CA
- Frank S. Chaves, Owner, Frank Chaves & Sons Dairy, Lodi, CA
- Grant Van Dyk, Co-Owner, Van Dyk Holsteins, Lynden, WA
- David H. Harris, Harris Livestock, Ashland, OH
- Charles J. Wampler, II, President, Hawk Valley Dairy, Inc., Fulks Run, VA
- Frank Carper, Cranbury, NJ
- Robert H. Klaus, Owner, Robert H. Klaus Farm, Carlinville, IL
- Robert F. Hilmes, Carlyle, IL
- Mervin M. Weaver, Johnsonville, IL
- David B. Hankal, Manager, Kephart Farms, Turlock, CA
- Ralph Vandyk, Owner, Vandyk Dairy, Meridian, ID
- Donald E. Taber, Owner, Donley Farms Inc.

These violations involved illegal residues of gentamicin in a dairy cow; sulfamethoxzole and streptomycin in a bob veal calf; penicillin in cows; oxytetracycline and gentamicin in a cow; gentamicin and penicillin in a cow; streptomycin in a cow; phenylbutazone in a cow; neomycin and sulfadimethoxine in a cow; streptomycin in a horse; sulfamethazine in a hog; penicillin and neomycin in a cow; and neomycin in a heifer calf.

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A warning letter was issued to the following firms for violations related to 21 CFR Part 589.2000—Animal Proteins Prohibited in Ruminant Feed. This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy (BSE).

- Arthur E. Bryan, Owner and Operator, Bryan Enterprises, Hanoverton, OH
- Edwin V. Ringer, Co-owner, Hartville Elevator Co., Inc., Hartville, OH
- Denny Hickman, President, Peco Foods, Inc., Tuscaloosa, AL
- John T. Dunbar, President, Champaign Landmark, Inc., Urbana, OH
- Donald and Lucy Hegge, Owners, Rietdyk's Milling Co., Ridgefield, WA
- Sam C. Shields, Owner, Shields Feed and Supply Co., Coffeeville, AL
- Robert C. Adams, Branch Manager, Western Reserve Farm Cooperative, Middlefield, OH
- John S. Wynkoop, President, Faler Feed Store, Inc., Lithopolis, OH
- Jerry and Helen Stewart, Owners, Stewart's Farm Supply, Brookville, NY
- Michael S. McCandish, Branch Manager, River Valley Co-Op, Baltimore, OH
- Robert W. Rudy, Vice President, Rudy, Inc., Covington, OH
- William D. Rohrbaugh, General Manager, Medina Landmark, Inc., Medina, OH
- Randall A. Hegenderfer, President, The Centerburg Mill and General Store, Inc., Centerburg, OH

Violations included lack of written procedures for cleaning out or flushing equipment after mixing feeds containing prohibited material; lack of documentation of steps taken to prevent cross-contamination; failure to identify the purchaser of feeds containing animal proteins by name and address; failure to track the use of prohibited materials from processing through distribution; and failure to label finished products with the required cautionary statement "Do Not Feed to Cattle or Other Ruminants."

Lawrence C. Brooks, DVM, Powder Ridge Veterinary Hospital, Middlefield, CT, received a warning letter as a result of an illegal gentamicin residue in a cow offered for sale and slaughter for human food. Dr. Brooks prescribed and dispensed the gentamicin for treatment of the cow's mastitis. Gentamicin is not approved for use in cattle, and there is no established tolerance for residues of gentamicin in the edible tissues of cattle.

Mr. Jean Michel Lopez, President, Micro Worldwide Trading, Miami, FL, received a warning letter for failure to ensure that imported products meet all requirements of the Federal Food, Drug, and Cosmetic Act. FDA attempted to examine a shipment of Ivomec animal antibiotic offered for entry into the U.S. by Micro Worldwide Trading, and found the entire shipment to be unavailable for FDA examination. The product was not held intact pending receipt of a "Release Notice" from FDA. FDA has requested the U.S. Customs Service to order redelivery of the animal antibiotic which had been distributed without a release from FDA.

Mr. Brian C. Langdon, President, New Decade Laboratories, Inc., Farmington, MN, received a warning letter for several deviations causing veterinary drugs manufactured at this facility to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Violations included the following:

- manufacturing and cleaning processes had not been validated;
- components, drug product containers, and finished drug products were not properly quarantined and tested;
- batch records lacked complete and accurate information concerning the production and control of drug products; and
- specifications for drug products were incomplete.

Mr. William Prestage, President, Prestage Farms, Inc., Clinton, NC, received a warning letter for violations including failure to conduct potency assays on at least three representative samples of each feed required to be manufactured by his licensed medicated feed mill at periodic intervals during the calendar year 2000, and failure to investigate and correct the cause of medicated feeds that failed assay specifications, and, failure to have master production records.

Mr. Brad Kerbs, President/CEO, Purina Mills, Inc., St. Louis, MO, received a warning letter for the facility located at Oklahoma City, OK, for significant deviations from Current Good Manufacturing Practice (CGMP) regulations for Medicated Feeds, 21 CFR Part 225. Violations included the failure to follow established SOP's for drug sequencing requirements, failure to conduct the required assays of medicated feeds for drug components, and failure to properly identify bulk drug components in a manner that assures their identity, strength, quality, and purity. In addition, the firm showed a continuing failure to ensure quality control over labeling operations for bagged medicated feeds since June 2000.

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CVM PLANS SECOND RISK ASSESSMENT ON THE USE OF ANTIMICROBIALS IN FOOD-PRODUCING ANIMALS

The Food and Drug Administration's Center for Veterinary Medicine (FDA's CVM) has decided to conduct a quantitative risk assessment on the human health impact of the development of the streptogramin (quinupristin/dalfopristin [QD]) resistant *Enterococcus faecium* in humans that is associated with the use of streptogramins (virginiamycin) in food-producing animals.

The drug Synercid™, a streptogramin (QD), was approved in September 1999 for the treatment of vancomycin-resistant *E. faecium* infections, as well as other gram-positive bacterial tissue infections in humans. Virginiamycin has been used for therapeutic and growth promotion purposes in chickens for 26 years. It has also been used for similar purposes in swine, cattle, and turkeys.

CVM initiated a feasibility study to determine whether sufficient data exist to support a quantitative model or if additional data need to be generated. On April 19, 2000, CVM announced the plan to develop the risk assessment (*http://www.fda.gov/cvm/antimicrobial/041900c.txt*), requested comments on the plan, and asked for the submission of relevant scientific data and information. This feasibility study has been completed, and CVM has determined that there are sufficient data either available or forthcoming to support a quantitative risk assessment of the human health impact from the use of virginiamycin in food-producing animals. Because some of the data needed for the risk assessment are currently under development, it will take a year or more to complete.

In January 1999, CVM released a discussion paper, *A Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals* (known as the Framework Document.) The Framework Document (*http://www.fda.gov/cvm/index/vmac/antimi18.html*) provides a conceptual risk-based framework for evaluating the risks to human health associated with the development of resistant bacteria arising from the use of antimicrobials in food-producing animals. Later in January 1999, FDA's Veterinary Medicine Advisory Committee discussed the Framework Document and heard from the public. Many comments from stakeholders asked that increased regulatory action not be implemented until risk assessments demonstrate a significant impact on public health (*http://www.fda.gov/cvm/antimicrobial/antimicrobial.html*).

CVM has completed a quantitative risk assessment that modeled the human health impact of fluoroquinolone resistant *Campylobacter* infections associated with the consumption of chicken (*http://www.fda.gov/cvm/antimicrobial/Risk_asses.htm*). It demonstrated the extent of the adverse impact of fluoroquinolone use in poultry on human health.

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NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 141-140)	Monensin (Coban®), Bacitracin Methylene Disalicylate (BMD®), Roxarsone	Chickens. For the prevention of coccidiosis, as an aid in prevention and control of necrotic enteritis and for increased rate of weight gain and improved feed efficiency.	**MEDICATED FEED**—The NADA provides for use of approved, single-ingredient monensin and bacitracin methylene disalicylate Type A medicated articles to make two-way combination drug Type C medicated feeds for broiler chickens and replacement chickens intended for use as caged layers. It is to be fed continuously as sole ration. It is not to be fed to chickens over 16 weeks of age or to laying chickens. *Federal Register* 03/05/01

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ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Med-Pharmex, Inc. (ANADA 200-299)	Ivermectin	Cattle. For treatment and control of various species of external and internal parasites.	**TOPICAL**—The ANADA is a generic copy of Merial Limited's Ivomec Pour-on for cattle, NADA 140-841. *Federal Register* 03/05/01
Phoenix Scientific, Inc. (ANADA 200-228)	Ivermectin (Phoenectin™)	Cattle, swine, reindeer, and American bison. For the treatment and control of various species of internal and external parasites.	**SUBCUTANEOUS**—The ANADA is a generic copy of Merial Ltd's Ivomec Injection, NADA 128-409. *Federal Register* 03/05/01

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SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Pennfield Oil Co. (ANADA 200-154)	Oxytetracycline (PENNOX™)	Beef cattle, non-lactating dairy cattle, and calves, including preruminating (veal) calves. For treatment of various bacterial diseases.	**SUBCUTANEOUS**—The supplemental ANADA provides for the subcutaneous administration of oxytetracycline injectable solution in cattle. *Federal Register* 03/05/01
Phoenix Scientific, Inc. (ANADA 200-193)	Clindamycin Hydrochloride Oral Liquid	Cats. For treatment of soft tissue and dental infections.	**ORAL**—The supplemental ANADA provides for the oral use of clindamycin hydrochloride liquid in cats. *Federal Register* 03/08/01

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SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Elanco Animal Health (NADA 104-646)	Monensin (Rumensin®), Tylosin (Tylan®)	Cattle. For prevention and control of coccidiosis, reduction of the incidence of liver abscesses, and improved feed efficiency.	**MEDICATED FEED**—The supplement provides for use of monensin and tylosin single-ingredient Type A medicated articles to make combination drug Type C medicated feeds for cattle fed in confinement for slaughter. The Type C medicated feeds are used for improved feed efficiency, prevention and control of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, and reduction of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes*. *Federal Register* 03/05/01
Novartis Animal Health US, Inc. (NADA 141-163)	Milbemycin Oxime (Milbemite™) Rx	Cats and kittens. To treat ear mite infections.	**OTIC**—The supplement provides for reducing the lower age limit from 8 weeks of age to 4 weeks of age and for repeating treatment one time, if necessary. *Federal Register* 03/08/01

(Continued, next page)

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Phoenix Scientific, Inc. (NADA 094-170)	Phenylbutazone Tab and Bolus	Dogs and Horses. For relief of inflammatory conditions associated with the musculoskeletal system.	**ORAL**—The supplement provides for oral use of a 200-mg strength tablet for relief of inflammatory conditions associated with the musculoskeletal system. *Federal Register* 03/12/01
Elanco Animal Health A Division of Eli Lilly & Co. (NADA 12-491)	Tylosin phosphate (Tylan®)	Cattle. For the reduction of the incidence of liver abscesses.	**MEDICATED FEED**—This supplement provides for the use of tylosin phosphate Type A medicated articles to make liquid Type B medicated feeds which are, in turn, used to make dry Type C medicated feeds for reduction of the incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes* in beef cattle. *Federal Register* 03/23/01
Elanco Animal Health A Division of Eli Lilly & Co. (NADA 104-646)	Monensin (Rumensin®), Tylosin (Tylan®)	Cattle. For the reduction of the incidence of liver abscesses, and for improved feed efficiency.	**MEDICATED FEED**—This supplement provides for use of Rumensin and Tylan Type A medicated articles to make liquid combination drug Type B medicated feeds which are, in turn, used to make dry Type C medicated feeds used for improved feed efficiency and reduction of the incidence of liver abscesses caused by *F. necrophorum* and *(Corynebacterium) pyogenes* in cattle fed in confinement for slaughter. *Federal Register* 03/23/01

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