FDA VETERINARIAN
Center for Veterinary Medicine
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FDA Prohibits Use of Human Anti-Viral Drugs in Poultry

The Food and Drug Administration (FDA) has issued an order that prohibits the extralabel use in poultry of two classes of approved human anti-influenza drugs to help preserve the effectiveness of these drugs for treating or preventing influenza infections in humans.

The order prohibits the extralabel use of anti-influenza adamantane (amantadine and rimantadine) and neuraminidase inhibitor (oseltamivir and zanamivir) drugs in chickens, turkeys, and ducks.

Extralabel use refers to the use of a human or animal drug that is beyond the scope of the approved labeling.

FDA has not approved any veterinary drugs for the treatment or prevention of influenza A in animals. However, two classes of antiviral drugs are approved in the United States for the treatment or prevention of influenza A in humans. Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA) veterinarians can legally prescribe extralabel uses of human and animal drugs in animals.

AMDUCA also gives FDA the authority to issue an order prohibiting certain extralabel uses in animals if such use presents a risk to public health. Concerns have been raised by a number of public health organizations, such as the World Health Organization, Food and Agriculture Organization, and the World Organisation for Animal Health, that the extralabel use of these human antiviral drugs in poultry could lead to the emergence of resistant strains of type A influenza. Avian influenza, including the H5N1 subtype, that has been identified in other countries is a type A influenza. Extralabel use of human antivirals in poultry could become a concern if highly pathogenic avian influenza emerged in the United States.

FDA has considered all available information and has concluded that the extralabel use of anti-influenza adamantane and neuraminidase inhibitor drugs in chickens, turkeys, and ducks presents a risk to public health. FDA may add other animal species to the prohibited list as new data become available.

When FDA issued the "Order of Prohibition," the Agency had not received any reports of extralabel use of these antiviral drugs in the United States by poultry producers.

The Order of Prohibition was issued as a final rule, as called for under AMDUCA, and scheduled to take effect June 20, 2006. Even though the order was issued as a final rule, interested parties may submit comments on this final rule by May 22, 2006. Comments may be submitted electronically through the Federal eRulemaking Portal: www.regulations.gov or to the Agency Web site: *www.fda.gov/dockets/ecomments*. Written comments may be faxed to 301-827-6870, or delivered by mail or hand to: Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. All comments must be identified by Docket No: 2006N-0106.

Background

Influenza viruses mutate frequently. Some mutations confer drug resistance to influenza viruses. Repeated and improper use of anti-influenza drugs could allow resistant influenza viruses to flourish. FDA is concerned with the ease in which influenza A viruses, which includes H5N1 avian influenza viruses, can become resistant to anti-influenza drugs after exposure. If influenza A viruses, which can infect humans, became resistant to the drugs currently available to treat them, the result would be a clear threat to human health.

In remarks prepared for a March 30 hearing of the House Agriculture subcommittee, Dr. Bruce Gellin, Director of the National Vaccine Program Office of the U.S. Department of Health and Human Services (the parent organization of FDA), described pandemic flu and explained why it was worse than more common types of flu.

Every year, Dr. Gellin explained, "seasonal flu" comes to the United States, infecting 5-20 percent of the U.S. population. The current strain of

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In This Issue

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

CVM Adverse Drug Data Show Increase in Reports of Lack of Effectiveness for Heartworm Prevention Drugs

by Dr. Martine Hartogensis, Veterinary Medical Officer, CVM Promotion and Advertising Liaison, Office of Surveillance and Compliance

The Center for Veterinary Medicine (CVM) has been receiving an increasing number of reports of lack of effectiveness in products designed to prevent heartworm disease in dogs and cats, and the best way to determine the reason for the increase is through more information that can come from routine heartworm tests and adverse drug event reporting.

The increase in the reports could be due to an increased awareness among veterinarians and pet owners about heartworm prevention effectiveness issues, leading to an increase in the number of reports while the incidence rate stayed the same. Or the increase might indicate a problem with the products.

CVM's database of post-approval Adverse Drug Experience reports currently includes 5,794 reports of lack of effectiveness for the heartworm prevention drugs. It could be that owners are not properly administering the drugs, or some dogs might not swallow the pills or could later vomit and lose the drug.

However, the database also includes 1,301 reports that CVM specialists have analyzed and determined to be definitely related to failure of the products. These cases were well documented concerning administration of the product according to the label, proper purchase history, and negative heartworm antigen tests prior to initiation of the drug and at least seven months after beginning prevention, followed by a positive antigen test.

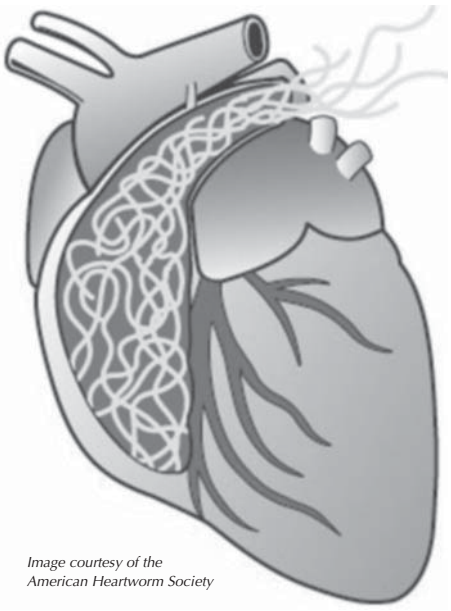

Image courtesy of the American Heartworm Society

Routine heartworm testing, as determined by the pet's primary veterinarian and discussion with the pet owner, can help protect the dog or cat. In addition, the tests can result in better information reaching CVM, generated through post-approval Adverse Drug Experience reports, so experts at the Center can determine why we are seeing an increase in lack of effectiveness reports.

Heartworm preventive medications intended for use in dogs and cats historically have been thought to be safe and effective. In fact, approval of a heartworm prevention product requires 100 percent efficacy in the pre-approval clinical trials.

However, the real world is not exactly like clinical trials. Real world conditions, such as patient variability, geographic considerations, and owner compliance, may be contributing to the effectiveness problems with these products.

In 2005, CVM's Division of Surveillance asked the sponsors of all marketed heartworm preventives to refrain

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FDA Prohibits Use... *(Continued)*

avian flu, H5N1, is highly contagious and lethal in chickens. In addition, it has been able to infect humans. However, the virus causing the current avian flu is not easily transmitted to humans, either from chickens or from an infected person to a healthy person.

"A pandemic flu is a new influenza virus strain for which humans have little or no immunity, and for which there is no available vaccine. The disease spreads easily person-to-person, causes serious illness, and can sweep across the country and around the globe in very short time," Dr. Gellin said.

He told the members of Congress at the hearing that "the medical and epidemiological community across the globe has studied structural changes in flu viruses and produced models based on historical pandemics that foreshadow an increasing science-based probability of a pandemic in the near future."

Information about the pandemic flu may be found at: *www.pandemicflu.gov*.

FDA VETERINARIAN

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CVM Improves Its Cumulative Adverse Drug Experience Summaries Website

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

There is a new look to the "Cumulative Adverse Drug Experience Summaries" on the Center for Veterinary Medicine's (CVM) website. The revised format should improve readers' interpretation of adverse drug experiences associated with specific animal drugs.

New animal drugs are evaluated for safety and effectiveness before they are approved by the Food and Drug Administration (FDA). However, testing is done in a limited number of animals and in controlled settings. Less common adverse drug events that could arise during real-world usage might not be detected during pre-approval testing. CVM scientists use reports of adverse drug experiences (ADE) to monitor a new animal drug after it is approved. The ADE reports are assembled into an ADE database. The ADE database helps CVM scientists decide whether there should be changes to product labeling or other regulatory action.

The reporting of ADEs has grown substantially in recent years due to greater awareness of the program and the approval of new types of animal drug products. For example, approximately

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CVM Adverse Drug Data Show Increase... *(Continued)*

from claiming 100 percent effectiveness in promotion and advertising materials, due to the number of post-approval reports of lack of effectiveness for all marketed preventive products.

Heartworm disease is transmitted to dogs and cats through mosquito bites. If the mosquito is carrying the heartworm larvae when it bites a pet, the disease is likely transmitted to the pet.

The larvae migrate throughout the tissues of the infected animal. Heartworm prevention products kill the larvae before they become adult worms. Without treatment, over the course of about six months the larvae mature into adult worms, with the male heartworm growing to 4-6 inches and the female growing to 10-12 inches. They reside in the animal's heart and lungs, and in nearby blood vessels. Even before they become mature, heartworms mate and produce microfilariae, which turn into larvae that ultimately become adult heartworms. The microfilaria must be ingested by a mosquito before continuing their life cycle.

Heartworms can kill a dog. More likely, though, heartworms will make dogs extremely sick. Dogs infected with heartworm can be successfully treated; however, such treatment may be inconvenient and emotionally stressful for the owner. If treatment is necessary, it is important to try to accomplish it with a minimum of harmful effects from the drugs and a tolerable degree of complications created by the dying heartworms. Heartworm infected dogs showing no signs or mild signs have a high success rate with treatment. Dogs with evidence of more severe heartworm disease can be successfully treated, but the possibility of complications and mortality are greater. The presence of severe heartworm disease within a patient in addition to the presence of other life-threatening diseases may prevent treatment for heartworm infection.

The best way to avoid the trouble is through proper care by the veterinarian, including routine testing. Testing is important even in dogs regularly treated with heartworm prevention products, due to the occasional reports of product ineffectiveness.

The American Heartworm Society, which was established in 1974 to generate and disseminate information about heartworm disease and treatment, has more information about the disease on its website, *www.heartwormsociety.org*.

The Heartworm Society mentions annual testing in a question-and-answer article on its website. Specifically, the Society says: "Annual testing for heartworm infection is now highly recommended. Even though heartworm preventives...are essentially 100 percent (effective) in preventing infection when administered according to instructions on the label, animals on heartworm prevention occasionally test positive for heartworms. This apparent lack of effectiveness is usually due to owner compliance failure, travel or relocation of the animal to an area of active heartworm transmission, or unknown (or misdiagnosed) prior infection. Annual testing gives owners peace of mind in knowing that their pet is free of heartworms, and in cases where the animal is infected, it assures them of early diagnosis of infection and maximal benefits from heartworm adulticide therapy."

If the use of a heartworm prevention product results in ineffective prevention for heartworms, the treating veterinarian or animal owner should file an Adverse Drug Experience report with the drug's sponsor, which should have its telephone number on the product's label. The company is required to provide CVM information from all Adverse Drug Experience reports. The veterinarian or owner can instead file a report directly with CVM by calling 1-888 FDA-VETS. More information about Adverse Drug Experience reporting is available at www.fda.gov/cvm/adetoc.htm.

CVM Improves... *(Continued)*

3,000 reports were submitted to CVM in 1995, compared with about 18,000 in 2000 and 33,500 in 2005.

Information in the ADE database has been summarized and made available to the public in various formats since 1989. Annual ADE summaries initially were included as inserts in the *FDA Veterinarian*. Beginning in 1999, ADE summaries for animal drugs have been posted on CVM's website. Most recently the ADE information has been presented on CVM's website as "Cumulative Adverse Drug Experience (ADE) Summaries," which include data collected since 1987.

Late in 2005, CVM decided to revamp the Cumulative ADE Summaries to allow readers a more accurate interpretation of ADE information. The Summaries were removed from the CVM website in December 2005, and the revised Summaries were rolled out on March 10, 2006.

How ADE summaries are generated

Over 99 percent of the information in CVM's ADE database results from an animal owner or veterinarian contacting the drug manufacturer directly and reporting an adverse event. A manufacturer's phone number typically will be on the drug's label. The manufacturer must complete and submit an "FDA 1932" form to FDA within 15 days for serious and unexpected adverse events, or in periodic reports to FDA for "expected" adverse events, e.g., where risk of the adverse reaction is described on product labeling. Manufacturers typically submit periodic reports to FDA every 6 months during the first 2 years after an animal drug is approved, and then annually.

Owners or veterinarians may instead report an adverse reaction directly to FDA using an "FDA 1932a" form. A 1932a form may be printed from the "Adverse Drug Reactions" link on CVM's website or may be requested by calling the Center (1-888-FDA-VETS). The 1932a form is pre-addressed and postage prepaid for mailing to CVM.

The 1932 and 1932a forms ask for detailed information on the drug and its usage, the treated animals, and the adverse event. Any information that owners or veterinarians can provide the drug manufacturer or CVM is useful. However, with more detail, CVM can better characterize the adverse event and determine how likely it was associated with the drug.

Summary score

CVM reviewers, who are experienced clinical veterinarians, evaluate information in ADE reports and score each "sign," or clinical manifestation seen in the treated animal, using a modified version of a human ADE algorithm. The scoring system takes into account previous experience with the drug, other possible causes, timing of events, evidence of overdose, whether the problem disappears after withdrawal of the drug, and whether the problem reappears when the drug is reintroduced. A summary score ranging from -9 to +7 is assigned to each clinical sign and corresponds to how likely it is associated with use of the drug. Clinical signs with summary scores of 0 or greater are considered "possibly, probably, or definitely" drug-related. Negative scores denote signs that are considered "remotely" drug-related or without enough evidence to draw a conclusion.

CVM reviewers enter the information and summary scores derived from ADE reports into the Center's ADE database. The Center also uses this information to update the Cumulative ADE Summaries available to the public, typically on a monthly basis.

Changes to the Cumulative ADE Summaries

The Cumulative ADE Summaries are on CVM's website at the "Adverse Drug Reactions" *http://www.fda.gov/cvm/adetoc.htm* link found either in the "Hot Topics" section or under the "CVM A-Z Index" of the home page. The Summaries are separated into alphabetical subsections at the bottom of the Adverse Drug Reactions page. Users click on the subsection associated with the generic name or active ingredient of the drug of interest. The page has a guide that allows users to find the generic name by looking up the brand name. A Summary is provided for a specific drug, species, and route of administration reported to FDA.

Drugs are listed in the Summaries by their generic, or active ingredient name. There may be more than one brand of the generic drug. A complete list of brand names associated with each generic name may be found using CVM's on-line "Green Book."

Until December 2005, each Summary listed at the top: "reviews" (number of ADE reports for this use of the drug); "treated" (number of animals in the reports that were treated with the drug); and "reacted" (number of treated animals in the report that had an adverse reaction assigned any summary score, i.e., from -9 to +7). These terms often were confusing unless readers referenced a glossary. Each Summary also listed at the top the number of animals in the ADE reports that "died." However, this term included incidents that CVM reviewers might determine were not "possibly, probably, or definitely" related to use of the drug, plus animals that were euthanized.

The previous version of each Summary listed by frequency every clinical sign and the number of treated animals observed with the sign "possibly, probably, or definitely" associated with this use of the drug (i.e., a summary score of 0 or higher). Also provided for each sign was the percent of all ADE reports for this use of the drug in which the specific sign was reported. These percentage terms were often misinterpreted as meaning the percentage of all animals in the United States receiving the drug that had this sign.

The new version of the Cumulative ADE Summaries now lists at the

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Cattle Reproductive Drug Estradiol Cypionate (ECP) Illegal, CVM Reminds Industry

The Center for Veterinary Medicine (CVM) in April issued a reminder to veterinarians and compounding pharmacies that estradiol cypionate (ECP) is not approved for use in cattle.

The Center has received reports that some veterinarians are using ECP that was compounded from bulk products for reproductive purposes in dairy and beef cattle. FDA has never approved the drug for veterinary uses.

Before 2003, a commercially marketed, unapproved ECP product was available. The manufacturer removed the product from the market when CVM asked the company to submit data in accordance with the drug approval process or to stop marketing it.

Since then, some veterinarians and veterinary drug compounders have continued to make a product for use in cattle. CVM officials say that the overall use of ECP has fallen off significantly since the company stopped marketing it, but has not ended completely.

Food and Drug Administration investigators are checking with compounding firms to find the source of ECP used for compounding.

Under certain circumstances, veterinarians can use drugs to treat conditions not listed on the approved label. The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 provides the legal basis for extralabel drug use. Using ECP to increase reproductive performance or production is not a permitted extralabel use under AMDUCA, CVM said. The extralabel use of drugs as provided for under AMDUCA is limited to FDA approved animal and human drugs, when the health or life of an animal is threatened.

The reminder to veterinarians, pharmacies, and others was issued as a "CVM UPDATE," which is available at *http://www.fda.gov/cvm/CVM_Updates/ECPup.htm*.

CVM Improves... *(Continued)*

top of each Summary the "Number of Animals Evaluated," which refers to the number of animals in the ADE reports for a specific drug, species, and route of administration that CVM scientists review for adverse reactions. The term places focus on the animals in the ADE reports, rather than the number of ADE reports submitted. CVM reviewers may determine that the adverse experiences in some of the animals evaluated were not "possibly, probably, or definitely" related to the drug.

The Summaries continue to list by frequency every clinical sign and the number of treated animals observed with the sign "possibly, probably, or definitely" associated with this use of the drug. However, the percentage term used previously has been dropped to avoid its misinterpretation as a percentage of all animals receiving the drug. Death is now included among the signs by order of frequency but is separated into appropriate categories, such as "death" and "death by euthanasia," to more accurately characterize the reaction.

Limitations

Despite the recent revisions, readers must still keep in mind the limitations of the Cumulative ADE Summaries.

The incidence rate or risk of specific clinical signs associated with a drug cannot be calculated because the total number of animals given the drug in the United States is not known. For this same reason, drugs listed in the ADE reports cannot be compared in terms of the number of clinical signs reported. If one drug is widely used, it may have more ADE reports than another drug used in only a small number of animals. Also, media attention to a specific drug might result in many more ADE reports being submitted.

The accuracy of ADE information in the cumulative reports is dependent on the quality of information CVM receives from veterinarians or animal owners. While valuable in terms of monitoring a drug in a real-world setting, the information can be less precise or specific than data coming from a controlled study.

Although the scoring algorithm helps CVM scientists estimate the likelihood of an association between a drug and a reported clinical sign, it cannot definitely show that an adverse reaction was caused by the drug. The adverse reaction may have been related to underlying disease, use of other drugs at the same time, or other non-drug related causes.

Comings and Goings

New Hires

OFFICE OF MANAGEMENT

- Christopher Louviere, Office Automation Clerk

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Nina Kaplan, Biologist
- Raanan Bloom, Physical Scientist

CVM Participation in Codex Alimentarius: Important for Food Safety as Well as for International Trade

by Merton Smith, Ph.D., J.D., Special Assistant for International Activities, Center for Veterinary Medicine

An important part of the regulatory work of the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) relates to the establishment of, and monitoring compliance with, appropriate food safety measures. Many of CVM's food safety controls are based on or are complementary to standards developed by the Codex Alimentarius Commission (CAC) *www.codexalimentarius.net*.

The CAC is an international body created to establish food standards with the dual goals of protecting the health of consumers and ensuring fair practices in the food trade. Sometimes, food standards include protective health measures that national governments use for import controls. Import regulations are often referred to as "non-tariff barriers" because they can function in a similar manner as tariffs to restrict trade. Non-tariff barriers may be meant to protect public health, but they can also be simply disguised barriers to trade. The standards of the CAC help prevent the use of non-tariff barriers to block trade.

The importance of the CAC as a food standards-setting organization was dramatically elevated with the April 15, 2004, signing in Marrakesh of the Final Act of the Uruguay Round of Multilateral Trade Negotiations. In addition to establishing the World Trade Organization (WTO) *www.wto.org*, the completion of the Uruguay Round included finalizing the Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement). This agreement concerns the application of SPS measures—in other words, food safety and animal and plant health regulations and controls.

The SPS Agreement recognizes that governments have the right to take SPS measures, but that those measures should be applied only to the extent necessary to protect human, animal, or plant life or health and should not arbitrarily or unjustifiably discriminate between WTO member countries where identical or similar conditions prevail.

In order to harmonize SPS measures on as wide a basis as possible, WTO member countries are encouraged to base their measures on international standards, guidelines, and recommendations where they exist. One of the international standards organizations specifically named in the SPS Agreement is the CAC. (The other organizations named are the International Office of Epizootics and the International Plant Protection Convention.)

WTO member countries such as the United States can have higher standards than those established by Codex, but there must be scientific justification and the standards must reflect consistent risk decisions based on appropriate risk assessments. The SPS Agreement spells out some basic procedures and criteria for the assessment of risk and the determination of appropriate levels of SPS protection.

It is also expected that WTO member countries will accept the SPS measures of others as equivalent if the exporting country demonstrates to the importing country that its measures achieve the importing country's appropriate level of health protection.

In addition, the SPS Agreement includes provisions on control, inspection, and approval procedures.

Scientific evidence as basis for Codex standards

Codex relies on scientific evidence and disciplined risk assessment procedures to make its decisions in establishing food safety standards. With respect to the safety of food additives and contaminants (including residues of animal drugs), the CAC routinely considers the recommendations of the Joint Expert Committee on Food Additives (JECFA). JECFA is jointly sponsored by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO).

JECFA draws its membership from standing expert advisory panels that are composed of independent scientists who serve in their individual capacities as technical experts and not as representatives of their governments or employers. The scientific caliber of WHO and FAO technical experts is outstanding. FDA and CVM toxicologists and chemists are among many of the well-qualified scientists that have served on these panels for decades.

These expert panels are convened according to the regulations governing the formation of expert advisory panels and committees of the FAO and the WHO, such as WHO's Expert Advisory Panel on Food Safety.

In general terms, the purpose and function of JECFA include:

- reviewing the latest knowledge and expert information on the safety of substances added to food,

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CVM Participation in Codex Alimentarius... *(Cont.)*

including food additives, residues of animal drugs in foods, and chemical contaminants in food, and making it available to FAO and WHO;

- formulating technical recommendations; and
- making recommendations designed to initiate, stimulate, and coordinate the research necessary to fulfill their terms of reference.

The JECFA members invited by WHO are primarily responsible for reviewing the toxicological, pharmacological, and related data and for estimating (where the data are scientifically sound) acceptable daily intakes (ADI) of substances added to food, which essentially represent the level an individual can consume over a 70-year life span without facing a significant food safety risk, and for establishing principles for toxicological evaluation and testing. The members invited by FAO are primarily responsible for preparing and reviewing the chemical specifications and analytical methodologies for the identity and purity of food additives, animal drug residues, and contaminant residues that have undergone toxicological evaluation.

When veterinary drugs are considered and the data are adequate, the JECFA members are responsible for estimating the maximum residue limits (MRLs) in foods of animal origin allowable under ADI limits when drugs are used in accordance with good practice in the use of veterinary drugs.

For veterinary drugs, the results of JECFA evaluations are forwarded to the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) for review and then to the CAC for acceptance.

According to the Director of CVM, Dr. Stephen F. Sundlof, the CAC is important to FDA and CVM, not only because of trade, but primarily for how it helps to assure the food safety of products consumed in the United States.

"Food products imported into the United States that meet Codex standards are less likely to present a food safety problem," Dr. Sundlof said. "Many countries that export to the United States rely on Codex standards extensively; some countries even simply adopt Codex standards as their own. If FDA can help to assure that Codex standards are relevant, based on the best science available, and that they represent the outcome of independent, objective judgment, FDA can help improve the safety of food worldwide," he added.

FDA officials, including Dr. Sundlof and others from CVM, have participated in Codex for many years and value this opportunity to influence the development of international food safety standards. About 10 years ago, when the WTO first went into operation and began relying on the Codex for food safety standards, CVM's participation in the Codex became even more important, according to Dr. Sundlof.

While FDA often adopts Codex food safety standards, it is not obliged to do so if those standards do not support the level of health protection that has been deemed appropriate by Congress as reflected in relevant legislation or by FDA through its rulemaking process. ■

Codex Committees

The decisions of the Codex Alimentarius Committee (CAC) are the result of activities that take place in a complex organization dominated by several committees (see table below). The General Subject Committees concern themselves with issues that cut across different product commodity types. These standing committees cover "horizontal" subjects, meaning subjects that apply to several different food commodities. The subjects for these standing committees include food hygiene, food import and export inspection and certification, food labeling, food additives and contaminants, and methods of analysis and sampling. One of the general subject committees, the Codex Committee on Residues of Veterinary Drugs in Food, is chaired by Center for Veterinary Medicine (CVM) Director Dr. Stephen F. Sundlof.

The Codex also has Commodity Committees that cover "vertical" or single commodity product classes, and Regional Committees covering subjects of interest in local geographic areas of the world. These are also standing committees, but CVM usually has little or no participation in them.

The CAC also utilizes temporary, issue-driven task forces. For instance, in 2005 the CAC re-engaged its Task Force on Foods Derived from Biotechnology, which is starting to focus on an important area for CVM—foods from genetically engineered animals.

Another Codex group of great importance to CVM, the Task Force on Animal Feeding, completed its work in 2004 by publishing a Code of

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Codex Committees *(Continued)*

Good Practice on Animal Feeding. However, the CAC is considering the possibility of re-establishing this group to deal with some additional issues of relevance to animal feeding.

The CAC is also likely to approve later this year the formation of a new task force that will deal with antimicrobial resistance issues.

Codex General Subject Committees

- General Principles
- Food Hygiene
- Food Import and Export Inspection and Certification Systems
- Food Labeling
- Food Additives and Contaminants
- Residues of Veterinary Drugs in Foods
- Pesticide Residues
- Nutrition and Foods for Special Dietary Uses
- Methods of Analysis and Sampling

Codex Commodity Committees

- Meat Hygiene
- Milk and Milk Products
- Fish and Fish Products
- Processed Fruits and Vegetables
- Fresh Fruits and Vegetables
- Fats and Oils
- Cocoa and Chocolate Products
- Vegetable Proteins
- Cereals, Pulses, and Legumes
- Sugars
- Natural Mineral Waters

Codex Regional Committees

- North America and the Southwest Pacific
- Europe
- Asia
- Latin American and the Caribbean
- Africa
- Near East
- Middle East

Codex Task Forces

- Foods Derived from Biotechnology
- Animal Feeding
- Fruit and Vegetable Juices
- Antimicrobial Resistance

Organizations Related to Codex

- Joint Expert Committee on Food Additives
- Joint Meeting on Pesticide Residues
- Joint Expert Meetings on Microbiological Risk Assessment

Observer Organizations Include

- World Trade Organization
- International Organization for Standardization
- International Commission on Microbiological Specifications for Foods
- Consumers International

The Codex Process

by Merton Smith, Ph.D., J.D., Special Assistant for International Activities, Center for Veterinary Medicine

Proposed Codex Alimantarius Commission (CAC) standards go through an eight-level process to be finalized.

In the first four steps, the CAC accepts a proposal for a standard and assigns the proposal to the appropriate committee to develop the details of a standard, and the committee sends the proposed standard to countries for review and comment and then incorporates the comments into a proposed standard. For Step 5 through 7, the CAC initially reviews the draft standard and sends it forward to member countries and Codex committees for review and comment.

The last step, Step 8, is the CAC's final review of the standard, followed by acceptance, modification, or rejection of the standard.

The development of food standards involves two CAC reviews, at Step 5 and 8. Even though the CAC is now meeting every year instead of every other year as in the past, the typical development of a Codex standard still takes a number of years to complete because of the complexity of this process.

Once the CAC establishes a standard for a substance, countries must consider accepting the standard. If a

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The Codex Process *(Continued)*

country does not accept a Codex standard and establishes a more stringent standard, it should be prepared to justify and adequately explain the scientific basis for the more stringent standard.

As described in the related story ("CVM Participation in Codex Alimentarius: Important for Food Safety as well as for International Trade" page 6), under the Sanitary Phytosanitary Agreement of the World Trade Organization (WTO), governments have the right to enjoy standards that are more stringent than Codex, but the standards must be applied only to the extent necessary to protect human health or safety and they should not arbitrarily or unjustifiably discriminate between other countries where similar conditions exist.

If a trading partner believes that a food standard that is more stringent than a Codex standard presents an unjustifiable barrier to trade, the trading partner may seek remedies through the WTO. That is precisely what happened leading up to the U.S.-European Union hormone trade dispute (see related article, "Beef Hormone Trade Dispute and Codex").

Beef Hormone Trade Dispute and Codex

by Merton Smith, Ph.D., J.D., Special Assistant for International Activities, Center for Veterinary Medicine

In 1985, the European Union (EU) enacted a ban on production and importation of meat derived from animals treated with growth-promoting hormones. The EU justified the ban as needed to protect the health and safety of consumers from the illegal and unregulated use of hormones in livestock production in several EU Member States.

On January 1, 1989, the EU banned the import of U.S. beef produced with growth-promoting hormones. This action dramatically reduced beef exports to EU Member States. The value of the lost exports was about $100 million. The United States retaliated by imposing 100 percent duties on $100 million in EU products exported to the United States. This retaliation continued with some adjustments during the period of 1989-1996.

In April 1996, the United States requested that the World Trade Organization (WTO) Dispute Settlement Body (DSB) establish a panel to consider the U.S. claim that "European Community measures against certain growth hormones (the six hormones involved in this dispute were estradiol-17, progesterone, testosterone, trenbolone, zeranol, and melengestrol acetate [MGA]; the first three are natural hormones and the second three are synthetic hormones) adversely affect imports of meat and meat products and appear[ed] to be inconsistent with the obligations of the European Communities under…the Sanitary and Phytosanitary (SPS) Agreement…."

In May 1996, a panel (the Hormones Panel, officially called "Panel on EC Measures Concerning Meat and Meat Products [Hormones])" was formed "to examine…the matter…and to make such findings as will assist the DSB in making the recommendations or in giving the rulings provided for in the SPS (and other WTO) agreements." In February 1997, the Hormones Panel consulted with scientific and technical experts and issued its final report in June 1997, in which it found that EC measures were inconsistent with the SPS Agreement.

(By way of background, the WTO's dispute resolution procedures permit a WTO Member government to request that a dispute resolution panel be established to determine whether measures maintained by another WTO Member government violate its obligations under the WTO agreements. Such a panel, normally consisting of three individuals selected in consultation with the parties to the dispute, considers written submissions and oral arguments by the parties. According to the applicable WTO procedures, a panel may seek advice from experts selected in consultation with the parties to the dispute, particularly in a dispute involving scientific or technical issues.)

Following an EU appeal of the initial findings of the Hormones Panel, in February 1998 the WTO Appellate Body upheld the Panel's findings that the EU was inconsistent with Articles 3.3 and 5.1 of the SPS Agreement.

Article 5.1 states that "Members shall ensure that their sanitary or phytosanitary measures are based on an assessment, as appropriate to the circumstances, of the risks to humans, animal or plant life or health, taking into account risk assessment techniques developed by the relevant international organizations." The EU was inconsistent with that article because it

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…Trade Dispute and Codex *(Continued)*

"maintained measures which were not based on a risk assessment," the panel said.

The panel also found that the EU was inconsistent with Article 3.3 of the SPS Agreement. That article says that "Members may introduce or maintain sanitary of phytosanitary measures which result in a higher level of sanitary or phytosanitary protection than would be achieved by measures based on the relevant international standards, guidelines, or recommendations, if there is a scientific justification, or as a consequence of the level of sanitary or phytosanitary protection a Member determines to be appropriate in accordance with the relevant provisions of paragraphs 1 through 8 of Article 5." The panel said that, "by maintaining sanitary measures which are not based on existing international standards without justification under Article 3.3 of the SPS agreement, it had acted inconsistently with the requirements…of that agreement."

Finally, after arbitration proceedings and other delays, in July 1999 the DSB authorized the United States to begin collecting tariffs, by suspending its concessions on $116.8 million worth of imports from the EU, the amount that it lost each year due to the hormone ban.

Following the findings of the Hormone Panel, the EU announced it would conduct additional studies and risk assessments on hormones that would satisfy its Article 5.1 obligations.

EU requests further hormone consultations

On November 8, 2004, the EU filed a request for consultations with the United States asserting that the United States should have removed its retaliatory measures because the EU believed it had now removed the measures found to be SPS-inconsistent by the Hormones Panel. Specifically, on October 14, 2003, the EU amended its Council Directive 96/22/EC concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists and asserted that it was now in conformity with the Hormones Panel. The EU further asserted that the amendment of Directive 96/22/EC was based on comprehensive risk assessments, in particular on the opinions of its Scientific Committee on Veterinary Measures relating to Public Health. Underpinning these risk assessments were a number of EU-funded and initiated studies and projects. The EU concluded that "the avoidance of intake of oestradiol 17ß is of absolute importance to human health and that, consequently, the placing on the market of meat containing this substance should be prohibited." With regard to the other hormones in dispute, the EU provisionally prohibited the placing on the market of meat containing these substances because the EU asserted that relevant scientific evidence was insufficient.

The United States disagreed and denied both that the new Council Directive 96/22/EC was based on science and that the Directive implemented the DSB's recommendations and rulings. The United States formally stated that it considered the new Directive to be inconsistent with the EU obligations under the SPS Agreement 5.1 and that it would continue to impose retaliatory duties on certain products from the EU. In January 2005, the EU requested the WTO to convene another dispute resolution panel.

The United States believes that, contrary to the EU's claim, there are no studies that demonstrate there is increased health risk from the consumption of meat from animals treated with growth-promoting hormones.

The first meeting of this new panel and the disputing parties took place in September 2005. To highlight the broad interest that this case continues to have, it is interesting to note that this has been the first time a WTO dispute panel meeting has been conducted and broadcast in full transparency. Initially the panel was expected to complete its work within six months, but several months ago determined that, "due to the complexity of the dispute and the administrative and procedural matters involved," it is not expected to issue a final report until October 2006.

This trade dispute has been ongoing for a number of years and has been rather bitter especially considering that it has involved a relatively small amount of trade. (For example, in 1999 the trade lost from hormone-treated beef amounted to less than 0.1 percent of all U.S. exports to the EU.)

Relying on JECFA, CCRVDF, and CAC

In this continuing hormone trade dispute with the EU, the United States has relied significantly on the safety decisions made by the Codex Alimentarius Commission (CAC), its Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF), and the Joint Expert Committee on Food Additives (JECFA), especially in pressing its case before the 1996 Hormones Panel.

For the six hormones at issue in this dispute, JECFA considered five of the substances (all except MGA) and made recommendations on four of them (excluding trenbolone) during its 32nd Session in 1987. For trenbolone, further data were sought, and a JECFA recommendation was made in 1989. The CCRVDF considered the JECFA recommendations at its meeting in 1987 and recommended draft standards for the

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...Trade Dispute and Codex *(Continued)*

three endogenous hormones and one of the synthetic hormones, zeranol. These draft standards were approved by the CAC at Step 5 in 1989. Standards for these four hormones were considered at Step 8 by the CAC in June 1991, but, following a vote on the matter, were not adopted. A draft standard for trenbolone at Step 5 was adopted on 1991.

In June 1995, the CAC adopted standards, at Step 8, for the five hormones (all except MGA), on the basis of a vote. These standards apply exclusively with respect to cattle and meat and meat products of bovine origin, when these hormones are used for growth promotion purposes.

For the three natural hormones in dispute, estradiol-17, progesterone, and testosterone, CAC considered it "unnecessary" to establish an Average Daily Intake (ADI) or Maximum Residue Level (MRL). Specifically, the CAC standard states:

"Establishing an ADI and an (MRL) for a hormone that is produced endogenously at variable levels in human beings was considered unnecessary by the Committee (CCRVDF). Residues resulting from the use of this substance as a growth promoter in accordance with good animal husbandry practice are unlikely to pose a hazard to human health."

Earlier, in the 32nd Report of the JECFA (1988 JECFA Report) on which the Codex hormone standards are based, JECFA concluded that residues arising from the use of testosterone and estradiol-17 as growth promoters in accordance with good animal husbandry practice are unlikely to pose a hazard to human health and that the amount of exogenous progesterone ingested in meat from treated animals would not be capable of exerting a hormonal effect, and therefore, any toxic effect, in human beings. (The term "good animal husbandry practices" is recognized to mean "the official recommended or authorized usage including withdrawal periods, approved by national authorities, of veterinary drugs under practical conditions." This is an important condition given that some of the EU concerns were raised with reference to the improper use of hormones.)

With respect to two of the synthetic hormones at issue, zeranol and trenbolone, the JECFA recommendations concluded that any toxic effects of these hormones are associated with their hormonal properties and that an ADI could thus be established on the basis of a no-hormonal-effect level. JECFA adopted what it considered to be a conservative approach by using animals highly sensitive to these hormonal substances and using a safety factor of 100.

For these two synthetic hormones the JECFA recommendations included the following: an ADI of 0-0.5 µg/kg body weight for zeranol and 0-0.0225 µg/kg body weight for trenbolone, and for both hormones an MRL of 2.25 µg/kg in bovine muscle and 10.25 µg/kg in bovine liver. According to JECFA, the MRLs thus obtained should not exceed the Codex ADI or safe level at any time after implantation of the drug, regardless of the withdrawal period used.

The CAC vote in 1995 adopting these JECFA recommendations about hormones was not unanimous. The CAC usually adopts its standards by consensus, but in this case consensus was not possible. The CAC adopted the hormone standards by a majority vote: 33 to 29, with seven countries abstaining.

The approval of these five hormones by the CAC provided important support for the United States in its subsequent case in the WTO against the EU.

Public health protection and the hormone trade dispute

It is clear from this dispute over the safety of hormones that Codex decisions can be used to either support or to lend non-support to national food safety control measures in trade disputes. But the primary interest of both the Food and Drug Administration (FDA) and the Center for Veterinary Medicine (CVM) in participating in the standard-setting activities of Codex and JECFA is to ensure that Codex decisions are based on sound science with the goal of protecting the public health.

FDA is not a trade facilitation or trade promotion arm of the U.S. Government, but many of FDA's decisions and actions clearly may result in effects on international trade for food and other products. Even though it is not a trade promotion agency, FDA does have a responsibility to explain the scientific and regulatory basis for its decisions and to provide evidence that the decisions are applied consistently to comparable risks. This kind of information is regularly given to U.S. trade protection or promotion agencies such as the U.S. Department of Commerce or the Office of the U.S. Trade Representative, as well as to foreign government and industry officials who ask for such information.

Furthermore, FDA has some responsibilities articulated in law to support U.S. trade agencies and some of their activities when they do not contravene FDA's public health purposes. Specifically, the Federal Food, Drug and Cosmetic Act's (FFDCA) section 803(c)(1) requires that "the Secretary shall support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in meetings with representatives of other countries to discuss methods and approaches to reduce the burden

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Federal Agencies Partner With Private Industry for Bioterrorism Vulnerability Assessment

by Jon F. Scheid, Editor

Four Federal Government agencies, including the Food and Drug Administration (FDA), have created the Strategic Partnership Program Agroterrorism (SPPA) initiative that allows them to work with industry volunteers and State agricultural and health counterparts to assess the potential risk from terrorist attacks against sectors of the agriculture and food industry. The first joint SPPA initiative exercise was held in December 2005 to examine the vulnerability of export grain elevators. The exercise was conducted at an export elevator outside of New Orleans, LA. Participants in this exercise included volunteers from the grain industry.

The SPPA initiative was first launched in 2005. Participants from FDA are CVM and the Center for Food Safety and Applied Nutrition (CFSAN). Along with FDA, participants include the Department of Homeland Security (DHS), the U.S. Department of Agriculture (USDA), and the Federal Bureau of Investigation (FBI).

Information developed from the exercise will be distributed to other members of the industry to allow them to protect themselves from a potential terrorism attack. Government officials plan to provide periodic classified briefings for industry, State, and Federal partners who have the necessary security clearances and to produce unclassified summary reports that will highlight cross-sector lessons learned and best practices. For security reasons, information from the final report disclosing a potential vulnerability will not be publicly released.

To conduct the evaluation, the SPPA team runs what is called a "CARVER+Shock" analysis, a tool that analysts use to determine the desirability of a target to terrorists. "It allows you to think like an attacker by identifying the most attractive targets for attack,"

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...Trade Dispute and Codex *(Continued)*

of regulation and harmonize regulatory requirements if the Secretary determines that such harmonization continues consumer protections consistent with the purposes of this Act. (2) The Secretary shall support the Office of the United States Trade Representative, in consultation with the Secretary of Commerce, in efforts 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 European Union and the United States. (3) The Secretary shall regularly participate in meetings with representatives of other foreign governments to discuss and reach agreement on methods and approaches to harmonize regulatory requirements;" and section 903(b)(3) of the FDCA concerning FDA's mission: "The Administration shall… participate through appropriate processes with representatives of other countries to reduce the burden of regulation, harmonize regulatory requirements, and achieve appropriate reciprocal arrangements."

Need for credible science-based rules

In the end, if the scientific basis of health and safety standards is perceived to be invalid, whether they are viewed as overly protective or not protective enough, there will be distrust by the public of the regulatory actions that are based on those standards. Failing credibility may also result in increased problems related to a growing lack of compliance by product manufacturers and users. For example, reports of illegal products being available on black markets in some countries may indicate, in addition to inadequate enforcement capabilities, that government regulatory requirements are viewed as arbitrary or scientifically unjustifiable. The availability and use of such illegal products clearly can greatly exacerbate potential public health problems.

(In 2001 Dr. Rainer Stephany of the National Institute of Public Health and the Environment in Bilthoven, the Netherlands, reported that in some EU Member States extended black markets exist, facilitating the use of between 35 and 55 illegal hormonally active growth promoters in farm animals.)

Strong science-based national requirements and international standards are, and will continue to be, the focus of CVM's work both in its domestic regulatory capacity and in its participation in the work of Codex and JECFA.

...Bioterrorism Vulnerability Assessment *(Continued)*

according to Donald A. Kautter, Jr., a counterterrorism specialist with CFSAN.

CARVER is an acronym of:

- Criticality – what effect would the attack have on public health or the economy?
- Accessibility – can a potential terrorist get to and from the target easily?
- Recuperability – does the target have the ability to recover from the attack?
- Vulnerability – how easily can a terrorist attack the facility?
- Effect – what would be the direct loss from an attack, measured in terms of lost production?
- Recognizability – how easily would a terrorist recognize that a facility would make a good target?

The "shock" part of the evaluation is a combination of health, economic, and psychological effects of an attack. In other words, this part of the review is an analysis of how of much of a psychological jolt an attack would cause.

FDA and USDA have used the CARVER+Shock assessment tool to evaluate the potential vulnerabilities of farm-to-table supply chains for various food commodities. Under SPPA, the tool is adapted to individual companies or commodity groups, according to Mr. Kautter.

Conducting an evaluation

Industry participants in SPPA initiative evaluations are volunteers. A trade association recruited the export elevator and other export grain companies that participated in the December evaluation.

Companies that volunteer to participate in an SPPA review get, as part of the process, free training in conducting a CARVER+Shock analysis and a better understanding of their vulnerabilities, Mr. Kautter said.

Once the volunteer and the commodity food group have been selected the date for an evaluation is set, and the advance logistical and administrative arrangements begin.

When the date for the evaluation arrives, a team made up of government and industry representatives goes to the site to begin the 2- to 5-day evaluation. The team typically includes representatives from FDA, USDA, DHS, FBI, and State departments of public health and agriculture. The industry is represented by officials of the participating company, five or six executives from other, similar companies, and representatives of the responsible trade association.

The agenda for the visit includes a review of the design flow diagram of the production process at the site, a CARVER+Shock analysis, and an assessment of the site's vulnerabilities. After the analysis, the team identifies mitigation steps and information gaps that need more research to address.

The SPPA initiative has several technical goals, but the overall aim is for private industry participants and government officials as well as State counterparts to better understand vulnerabilities and identify mitigation steps for industry subsectors. Government specialists use the findings from the assessments, such as the export grain elevator review in December, to create lessons learned and best practices that can be applied to other companies within the subsector, and to improve the National Infrastructure Protection Plan, which is a blueprint of ways to protect against terrorism within the 17 critical infrastructures and key resources.

Another, broader goal is the establishment or strengthening of a working relationship including Federal, State, and local governments and private sector companies.

Feed manufacturers recruited

The SPPA assessment at the export elevator was one of many evaluations that the Federal agencies want to accomplish. The four government agencies have identified more than 60 other types food and agriculture facilities for analysis under SPPA, including animal feed manufacturers (which the officials hope to do next); animal byproduct manufacturers; corn refiners; beef cattle feedlots; poultry farms; cereal manufacturers; fluid milk and infant formula manufacturers; and produce processors.

The government SPPA team is currently looking for a feed industry volunteer for the next analysis. It would be conducted in much the same way as the grain export elevator assessment, Mr. Kautter said.

Agricultural companies that would like to participate in an SPPA evaluation can contact their representative trade association or can get more information on the SPPA page of FDA's website, *http://www.cfsan.fda.gov/~dms/agroterr.html*.

Ask CVM

Are mail order pet medications the same as those I get directly from the veterinarian?

As Internet technology becomes increasingly used to market consumer products, FDA has noticed more FDA-regulated products promoted and sold on line. In most cases, these activities are as legitimate as any other business activity conducted in traditional ways, but we have encountered unscrupulous and fraudulent practices.

FDA is aware that some people or firms are selling prescription drugs without a legitimate prescription, misbranded products with unsubstantiated claims, or unapproved or illegal products.

The FDA has prepared a webpage containing information about purchasing medicines and medical products on line. The URL for the website is: *http://www.fda.gov/oc/buyonline/*.

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Ask CVM *(Continued)*

I need a drug to treat my pet that you can't buy in the United States, but it is available overseas. How can I get permission to import that drug?

All requests to import medication for pets must come directly from the veterinarian treating the animal. The veterinarian must provide certain information to CVM so it can evaluate the request. CVM will send a document outlining the information needed to allow the importation to occur to any veterinarian inquiring about obtaining unapproved new animal drugs from non-U.S. sources. The veterinarian will be asked to provide information that identifies who he or she is, describe the disease or condition to be treated, the reasons why available products will not work, the legal status of the drug in a foreign country, and an exact specification of the product the veterinarian wants to import.

A letter of non-objection is prepared if the request is considered appropriate and reasonable. If the request is received via fax, a copy of the letter of non-objection is often faxed back. CVM also mails a hard copy of the letter of non-objection to the veterinarian.

The process can take three weeks or longer, depending on the volume of such requests that CVM received. The Center averages almost 50 letters a week

I found the same drug my veterinarian sells me, but for a much lower price in another country, and I can order it online. Do I need permission from FDA to import that drug?

Importing an animal drug that is available in the United States is illegal, and CVM cannot grant you permission to import it. CVM's regulations do not recognize cost or different marketing status (over the counter versus prescription, for instance) as a reason to allow imports of drugs. However, if the drug you want to import has an attribute not found with the drug available in the United States, such as a different dosage form (liquid versus tablet) or different strength or concentration, CVM might grant your veterinarian permission to import that drug. Decisions are made on a case-by-case basis.

Do I contact CVM if I have a concern about my vet, such as his treating my dog with drugs not approved for dogs, or the fact that he makes me buy drugs from him because he won't write a prescription the way my doctor will.

FDA does not regulate the practice of veterinary medicine. Writing prescriptions, etc., is considered the practice of medicine. Pet owners may contact the veterinary licensing board in their States to file a complaint about the practices of their veterinarians. This is a link to the listing of State veterinary licensing boards—*http://www.aavsb.org/*

To address the specific concerns raised in this question, veterinarians have the legal right to prescribe a drug for a dog even if the drug is not labeled for use in dogs. A 1994 law, the Animal Medicinal Drug Use Clarification Act, gives veterinarians the right to use any legally obtained human or animal drug in an "off-label" manner in pets, under certain conditions. For instance, the veterinarian must have firsthand knowledge of the animal's medical condition and must be available to handle any follow-up treatment or address any adverse reaction to the drug.

In addition CVM does not address issues about how animal drugs are sold to customers, beyond classifying the drugs as over-the-counter or prescription. Veterinarians are not prohibited from selling drugs to treat animals. At the same time, veterinarians are not required to sell drugs to animal owners. Some write prescriptions that the animal owner gets filled the same way a prescription for a human drug is filled.

Who in FDA should I notify if I think there is something wrong with my dog's commercially made pet food?

You should contact the FDA Consumer Complaint Coordinator for your State. Information for FDA Consumer Complaint Coordinators is available on FDA's website, *www.fda.gov*

I've seen several food additive products that are supposed to make my dog feel better. Does CVM regulate these products?

Yes, CVM regulates them and companies that market pet food supplements should not be making any health claims about the products, i.e., claims that the product works to reduce or eliminate conditions suffered by a pet, or that the product does anything other than supply nutritional components. Under current law, dietary supplements for animals are not recognized as a class of products. Products for animals are either foods or drugs.

Under the Dietary Supplement and Health Education Act (DSHEA), some human food products are considered to be dietary supplements rather than food additives or drugs. However, FDA has determined that DSHEA was not intended and does not apply to animal feed, including pet food. Thus, products marketed as dietary supplements or "feed supplements" for animals still fall under the Federal Food, Drug, and Cosmetic Act (the Act) prior to DSHEA, i.e., they are considered "foods," "food additives," or "new animal drugs" depending on the intended use.

Under the Act, expressed or implied claims that establish the intended use of a product to cure, treat, prevent, or mitigate disease, or affect the structure/function of the body in a manner other than food (nutrition, aroma, or taste), indicated that the product is being offered as a "drug." Unless the "drug" product has been shown to be safe and effective for its intended use via approval of a New Animal Drug Application (NADA), it could be subject to regulatory action as an adulterated drug. Certain substances have been marketed as nutritional supplements. However if there is no known nutritional requirement for the compound, it cannot legally be marketed as a nutritional supplement for animals.

I read in a magazine that I can contact CVM for free health care advice about my pet. Who do I talk to?

The Center continuously receives calls from individuals seeking free health care information about pets or financial assistance in providing veterinary care

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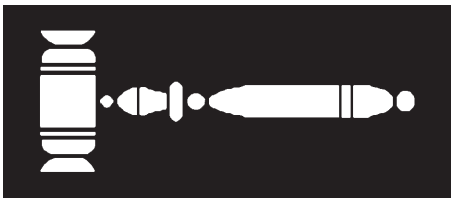
Regulatory Activities



A Warning Letter was issued to Jerry N. Meissner, president, Norm-E-Lane, Inc., Chili, WI, because an investigation confirmed that the dairy operation offered a dairy cow for sale for slaughter as food that was adulterated because of the presence of the new animal drugs sulfadimethoxine and penicillin G procaine in excess of the tolerances set forth in 21 CFR 556.640 and 21 CFR 556.510. The inspection also revealed that these new animal drugs were caused to be adulterated and unsafe. The investigation also found that the facility held animals under conditions that are so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. The operation lacked an adequate system to ensure that medicated animals were withheld from slaughter for the appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues. For example, the dairy operation lacked an adequate monitoring system to ensure that medications are administered to the designated animal. Food from animal held under such conditions is adulterated.

A Warning Letter was issued to Steven J. Silver, president, International Nutrition, Inc., Omaha, NE, because an investigation of the medicated feed mill and drug manufacturing site found a significant deviation from the Current Good Manufacturing Practice (cGMP) regulations for medicated feeds. Such a deviation causes the feed being manufactured at this facility to be adulterated. The investigation found that the firm failed to implement adequate safeguards to prevent unsafe contamination in the production of feeds. A calf vitamin/mineral product was manufactured following the production of a Category II, Type B medicated feed, Carbadox. An analysis of a Food and Drug Administration (FDA) sample found 170 ppm and 25 ppm in two of the 10 sub (samples) collected during the investigation. Carbadox is not approved for use in cattle feed. Also, Arsanilic Acid 4.5g/lb. was manufactured by sequencing after Arsanilic Acid 90g/lb. Assay of Arsanilic Acid 4.5g/lb. found it to be 131 percent, which is outside of the allowable assay limits of 85-115 percent. The investigation into the cause of the out-of-limits assay concluded carryover from the production of the Arsanilic Acid 90g/lb. was a likely cause. In addition, several labeling deviations were observed that cause certain feed products manufactured by the firm to be adulterated. Product labels for ZINPRO Corporation products containing the statement "Manufactured By ZINPRO Corporation" when the products are manufactured by International Nutrition Inc. for ZINPRO Corporation was observed. Also, the distribution of Type A medicated articles to consignees from whom the firm did not obtain an unrevoked written statement caused the new animal drug to be deemed unsafe and, thus, adulterated. In addition, the investigation found that labels for feeds containing procaine penicillin and decoquinate, for use in poultry laying hens and sheep, respectively, are not in conformance with the approved new animal drug applications. The approval for procaine penicillin provides that feed be labeled with a warning against use in poultry laying eggs for human consumption. The approval for decoquinate provides that feed be labeled with a warning against use in sheep producing milk for food. Labeling these products without the required warning statements causes these feeds to be unsafe and, thus, adulterated. It was also determined that the firm has not maintained in its possession the New Animal Drug Application approved labels as required by 21 CFR 510.305.

Ask CVM *(Cont.)*

for their pets. As a regulatory agency, CVM cannot offer pet health care advice or financial assistance.

The calls were prompted by a publication that said, erroneously, that CVM offered such assistance. We have contacted the publisher and asked it to stop publishing the incorrect information.

CVM has some fliers on pet care that can be found on its Home Page at: *http://www.fda.gov/cvm/consumer.html*.

Animal Drug Approvals for February 2006

CVM has published in the *Federal Register* notice of the approval of this New Animal Drug Application (NADA)

EQUIOXX (firocoxib) Oral Paste (NADA 141-253), filed by Merial Ltd. The NADA provides for veterinary prescription use of firocoxib oral paste in horses for the control of pain and inflammation associated with osteoarthritis. Notice of approval was published February 3, 2006.

(Continued, next page)

Approvals for February 2006 *(Continued)*

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

DURALEASE (estradiol benzoate) Microencapsulated Suspension Implant (NADA 141-040), filed by PR Pharmaceuticals, Inc. The supplemental NADA provides for subcutaneous injection, in the ear only, of a suspension implant of estradiol benzoate microspheres for increased rate of weight gain in suckling beef calves. It also adds the indication for use for increased rate of weight gain in steers fed in confinement for slaughter, previously approved at a lower dose, to the higher approved dose level. Notice of approval was published February 17, 2006.

CYDECTIN (moxidectin) Injectable Solution for Beef and Nonlactating Dairy Cattle (NADA 141-220), filed by Fort Dodge Animal Health, Division of Wyeth. The supplemental NADA provides for use of an injectable moxidectin solution in cattle for the treatment and control of an additional three species of internal parasites and an additional three life stages of previously approved internal parasites. The six new therapeutic claims are for: *Trichostrongylus colubriformis* – Adult; *Cooperia pectinata* – Adult; *Cooperia spatulata* – Adult; *Nematodirus helvetianus* – Adult; *Ostertagia ostertagi* - L_4; and *Trichostrongylus axei* - L_4. Notice of approval was published February 13, 2006.

DRONTAL PLUS (praziquantel/pyrantel pamoate/febantel) Taste Tabs for Dogs (141-007), filed by Bayer HealthCare LLC, Animal Health Division. The supplemental NADA amends the approved NADA by adding a flavored chewable tablet formulation with the same indications. The tablets are indicated for the removal of Tapeworms (*Dipylidum caninum, Taenia pisiformis, Echinococcus granulosus,* and removal and control of *Echinococcus multilocularis*) and for removal of Hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), Ascarids (*Toxocara canis, Toxascaris leonina*) and Whipworms (*Trichuris vulpis*) in dogs. Notice of approval was published February 9, 2006.

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