July/August 2001
Vol. XVI, No. IV

FDA VETERINARIAN

RISK ASSESSMENT ADVISOR COMES TO CVM

H. Gregg Claycamp, Ph.D., CHP, joined FDA's Center for Veterinary Medicine (CVM) as the Senior Advisor for Risk Assessment on June 4, 2001. Dr. Claycamp will help develop the antimicrobial risk assessment policy for CVM using state-of-the art science. He will also serve as the senior scientist for CVM's Office of New Animal Drug Evaluation (ONADE) in all other risk assessment issues.

Dr. Claycamp comes to CVM from the University of Pittsburgh, Graduate School of Public Health, where he was a Professor in the Department of Environmental and Occupational Health. At the University of Pittsburgh, Dr. Claycamp directed the graduate programs in Risk Assessment and Radiation Health while maintaining an active research and teaching career. His research has included international studies in radiation risk assessment, chemical hazard identification, environmental exposures, and basic studies on radiation or chemically induced DNA damage in both microbes and animal cells. Dr. Claycamp has developed novel applications of artificial intelligence for diverse problems in human health risk assessment.

H. Gregg Claycamp, Ph.D., CHP

Dr. Claycamp holds an A.B. degree in Human Biology from Stanford University and M.S. and Ph.D. degrees in Radiological Health Engineering from Northwestern University. Dr. Claycamp has served on the faculties of the University of Iowa College of Medicine and The University of Kansas Department of Radiation Biophysics. He has been involved in faculty governance and both national and university service committees including NIH, DOE and NSF peer-review committees, university committees having oversight of biohazard and radiation safety, and the Risk Assessment Committee for the American Industrial Hygiene Association.

Dr. Claycamp participates in many professional organizations including the Health Physics Society, Society for Risk Analysis and the Risk Assessment and Policy Association. He has served as chapter president for both the Health Physics Society and the Society for Risk Analysis. Dr. Claycamp is certified in the comprehensive practice of health physics by the American Board of Health Physics (Certified Health Physicist.) □

FDA SPONSORS NARMS SCIENTIFIC MEETING

by Marcia L. Headrick, D.V.M., M.P.H.

The FDA's Center for Veterinary Medicine (CVM) along with the USDA and CDC sponsored a two-day meeting on the results from the National Antimicrobial Resistance Monitoring System – Enteric Bacteria (NARMS – EB) and related antimicrobial resistance research. The meeting was held March 15 and 16, 2001, in Rockville, MD. The open scientific meeting was attended by over 200 registrants including representatives from Federal and State government agencies, academia, industry, commodity groups, public interest groups, and others interested in antimicrobial resistance research.

Dr. Linda Tollefson, Deputy Director, CVM, opened the meeting. Dr. Marcia Headrick, CVM NARMS Coordinator, organized the meeting. Members of the CVM Division of Epidemiology staff and other CVM staff were instrumental in the planning and coordination of the meeting. Representatives from FDA, USDA, and CDC served as moderators for the meeting and gave several of the presentations. The purpose of the meeting was to provide an opportunity for presentation of the results of antimicrobial research including results from the NARMS program.

(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

FDA SPONSORS NARMS SCIENTIFIC MEETING (Continued)

The meeting was composed of seven sessions including two sessions on *Salmonella* resistance research and one session each on Government Agency Sponsored Research, Mitigation Strategies, *Campylobacter*, Environmental Issues, and Commensal Resistance Research. Twenty-four speakers were included in the agenda.

A poster session was coordinated by Dr. Charlotte Spires, Acting Director, CVM Division of Epidemiology. Poster titles included:

- Presence of Enterococci on Grocery Products and Their Resistance Patterns
- Antimicrobial Resistance of *Salmonella* Isolates Collected from Swine Farms with Different Antimicrobial Use Programs
- Occurrence of Food Borne Pathogens and Antimicrobial Resistance Factors in Wild Turkeys
- Antimicrobial Resistance In *Salmonella* Isolates from Exotic Animals,
- NARMS 1997-1999
- Changes in Antimicrobial Resistance in *Campylobacter* Isolated from Chicken Carcass Rinses from 1998 to 2000
- Changes in Antimicrobial Resistance Profiles of *Campylobacter* Isolates – 1994/95 and 2000
- Antimicrobial Resistance in *Campylobacter* Isolated from Feedlot Cattle
- *Salmonella ser. Newport* in Georgia
- Metabolism and Fate of Ceftiofur used in Food Animals
- Quinolone/Fluorquinolone Resistance in Veterinary Isolates of *Salmonella enterica*
- Characterization of Multiple Drug Resistant *Salmonella Newport* Strains
- Detection of Antibiotic Resistance Emerging from Natural Mutator Strains Using Kirby Bauer and Broth Dilutions Antibiotic Sensitivity Assays
- Antimicrobial Resistance Among Enteric Bacteria Isolated from Human and Animal Wastes and Impacted Surface Waters: Comparison with NARMS Findings
- Antimicrobial Susceptibility Testing of *Campylobacter* Isolated from Retail Meats by Agar Dilution and E-test.

Poster abstracts and presentation slides will be posted on the CVM NARMS website. Related meetings were held by CDC in 1999 and by USDA in 1998. The next meeting will be hosted by USDA, Agricultural Research Service, Antimicrobial Resistance Research Unit (ARRU) which

(Continued, next page)

ANTIMICROBIAL RESISTANCE IN SALMONELLA ISOLATES FROM EXOTIC ANIMALS, NARMS 1997-1999

by M.L. Headrick (FDA-CVM, Athens, GA), L.A. Walker (FDA-CVM, Rockville, MD), and P.J. Fedorka-Cray (USDA-ARS-ARRU, Athens, GA)

The following is an abstract from a poster presented at the NARMS Scientific Meeting held March 15-16, 2001, in Rockville, MD.

ABSTRACT

One of the leading causes of acute gastroenteritis is infection with *Salmonella* species. The incidence of human salmonellosis infections associated with exposure to reptiles has increased in recent years and is partly attributed to the steadily increasing importation of Iguanas. Exotic pets appear to carry salmonellae as a commensal and are typically not treated when *Salmonella* is recovered. As part of the National Antimicrobial Resistance Monitoring System (NARMS), we collected *Salmonella* isolates from diagnostic laboratories that were associated with recovery from exotic animals. Isolates were tested using a Sensititre™ custom designed microtiter plate to determine minimal inhibitory concentrations (MICs) for 17 antimicrobials. More resistance was observed in 1997 and 1999, which may be attributed to the higher number of isolates tested. Resistance, although minimal, was observed for Ampicillin, Kanamycin, Nalidixic Acid, Streptomycin, Sulfamethoxazole, Tetracycline, Ticarcillin (not tested in 1999) and Trimethoprim Sulfamethoxazole. The most frequent serotype recovered in each year was *S. arizonae* and resistance was noted for all three years. A wide number of other serotypes were recovered each year but no other serotype was recovered in each of the years. These data suggest that resistance is low among *Salmonella* serotypes associated with exotic pets. This increases the likelihood that patients requiring antimicrobial treatment for severe or septic salmonellosis will not be compromised. However, continued monitoring is warranted.

Dr. Headrick is an Epidemiologist with CVM's Division of Epidemiology stationed in Athens, Georgia. Dr. Walker is a Veterinary Medical Officer with CVM's Division of Epidemiology. Dr. Cray is Research Leader with USDA's, Antimicrobial Resistance Research Unit, Athens, Georgia. □

FDA Veterinarian

Bernard A. Schwetz, D.V.M. , Ph.D.
Acting Principal Deputy Commissioner of Food and Drugs

Stephen F. Sundlof, D.V.M., Ph.D.
Director
Center for Veterinary Medicine

Karen A. Kandra, Editor

Published bi-monthly.

Home Page: http://www.fda.gov/cvm/

Articles are free of copyright and may be printed.

Comments are invited.

Phone (301) 594-1755

FAX (301) 594-1831 or write to:
FDA Veterinarian (HFV-12)
7500 Standish Place
Rockville, MD 20855

conducts the animal arm of the NARMS.

Registrants were asked to provide an evaluation of the 2001 NARMS Scientific Meeting. Information received from the evaluations will be analyzed and provided to Dr. Paula Cray, Research Leader of the ARRU, for use in planning the next meeting.

The NARMS program plays an important role in the overall understanding of antimicrobial drug resistance. The NARMS primary role is to provide descriptive data on the extent and temporal trends in antimicrobial susceptibility in *Salmonella* and other enteric organisms from human and animal populations. However, NARMS also facilitates the identification of resistance in humans and animals as it arises, provides information on antimicrobial resistance to veterinarians and physicians, prolongs the life span of approved drugs by promoting the prudent and judicious use of antimicrobial drugs, and identifies areas for more detailed investigation. NARMS also aids in antimicrobial resistance research by providing a national source of enteric bacterial isolates that may be invaluable for research such as diagnostic test development, discovering new genes and molecular mechanisms associated with resistance, studying mobile gene elements, and for virulence and colonization studies.

For more information on the NARMS program, please contact Dr. Marcia Headrick of FDA, CVM via e-mail *mheadric@cvm.fda.gov,* or call (706)546-3689. Additional information on the NARMS program is also available on the CVM NARMS web page at *http://www.fda.gov/cvm/index/narms/narms_pg.html.* A brochure on the NARMS program is available by contacting the *FDA Veterinarian* at (301) 594-1755.

Dr. Headrick is an Epidemiologist with CVM's Division of Epidemiology. She is the FDA/CVM NARMS Coordinator. □

COMPLIANCE POLICY GUIDE IN EFFECT FOR THE EXTRA-LABEL USE OF MEDICATED FEEDS IN MINOR SPECIES

by Meg Oeller, D.V.M.

The FDA has published a new Compliance Policy Guide (CPG), effective April 23, 2001, to allow for regulatory discretion for the extra-label use of medicated feeds in minor species (any species other than cattle, horses, pigs, dogs, cats, chickens, or turkeys).

A CPG is FDA's direction to its field inspectors. It describes the actions that they should take when they encounter a given situation. This CPG lets inspectors know that FDA will not ordinarily take regulatory action against producers, veterinarians, or feed mills who use or produce medicated feeds for extra-label use in minor species. This does *not* make the use legal. It simply means that, at this time, the FDA has chosen not to take action when medicated feeds are used under the conditions described in the CPG.

The full text of the CPG is the version that you should consult. This announcement is only intended to make you aware that this policy is in effect and to point out some of the more significant provisions.

A copy of the full text of the CPG is available on the FDA Home Page at: *http://www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg615-115.html*. If you prefer a paper copy, you may submit a written request for a copy of CPG number 615.115 to the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855. Please send one self-addressed adhesive label or envelope with your request.

"Extra-label use" refers to the use of an approved medicated feed in a manner that is not in accordance with the approved labeling. Extra-label use includes, but is not limited to use in a species not listed in the labeling, use for indications (diseases or other conditions) not listed in the labeling, and deviation from the labeled withdrawal time.

Some of the most significant provisions of this CPG include:

- The policy applies only to minor species.
- The medicated feed must already be approved for use in a major species.
- The feed must be formulated and labeled at the feed mill according to its approved labeling for the major species.
- If the medicated feed is to be used for a food-producing minor species, the medicated feed must be one approved for use in another food-producing species.
- If the medicated feed is to be used in an aquaculture species, the medicated feed must be one approved for use in another aquaculture species.
- The policy applies to farmed wildlife species, but not to unconfined wildlife.
- The medicated feed may be used in an extra-label manner only under the written recommendation and oversight of a licensed veterinarian.
- Only therapeutic extra-label uses of medicated feed are included. This excludes production claims such as increased weight gain or feed efficiency.
- The specific responsibilities of the animal producer, veterinarian, and the feed mill are all outlined in the text of the CPG.
- If the conditions of the CPG are not met or if tissue residue violations

(Continued, next page)

COMPLIANCE POLICY GUIDE IN EFFECT . . . (Continued)

occur, then regulatory action may be taken against the producer or the veterinarian, or in some cases against the feed mill.

The FDA hopes that this new CPG will enable minor species producers to more easily treat their animals when they are sick. This policy is intended to make many drugs approved for use in other species, available to these producers. This does not lessen the FDA's intent to encourage sponsors to seek full approvals specifically for minor species. A CPG may be withdrawn at any time, so an approval is still the best guarantee for the legal availability of needed medications.

If you have questions about this policy, you may contact: Fran Pell, FDA, Center for Veterinary Medicine, HFV-235, 7500 Standish Place, Rockville, MD 20855, (301) 827-0188.

Dr. Oeller is a Veterinary Medical Officer in CVM's Office of the Director, and the FDA liaison to NRSP-7 (the USDA's minor species program). □

FDA APPROVES FIRST INJECTABLE HEARTWORM DRUG FOR DOGS

FDA has approved the first injectable drug to prevent heartworm disease in dogs. One injection provides six months of heartworm protection. The drug, ProHeart® 6 (Moxidectin Sustained Release Injectable for Dogs), is an alternative to currently available heartworm prevention drugs that must be given on a monthly or daily basis.

Photo by Barbara Miller

Heartworm disease is a serious and potentially fatal condition of dogs, cats, and other species of mammals. The parasite that causes heartworm disease is Dirofilaria immitis. It is transmitted through the bite of a mosquito. The adult stage of the parasite is found in the heart and major blood vessels of infected animals.

Canine heartworm infection has been found in dogs in all 50 States. All dogs regardless of their age, sex, or habitat are susceptible to heartworm infection. The highest infection rates (up to 45%) in dogs not maintained on heartworm preventive are found within 150 miles of the Gulf of Mexico and Atlantic Coast from Texas to New Jersey and along the Mississippi River and its major tributaries. Other areas of the United States have lower incidence rates (5% or less) of canine heartworm disease.

Fort Dodge Animal Health, Fort Dodge, Iowa, is the manufacturer of ProHeart 6 and it will be available by prescription from a licensed veterinarian. It is approved for use in dogs six months of age and older and also treats existing hookworm (Ancylostoma caninum) infections. □

COMPANION ANIMAL ANESTHETIC APPROVALS

by Germaine Connolly, D.V.M.

The approval of three original New Animal Drug Applications (NADAs) for propofol (2) and sevoflurane (1) have provided new anesthetic drugs available for use in dogs. This article describes study designs that resulted in the generation of satisfactory data used for these approvals. Results are not presented, but are available to the public in the Freedom of Information (FOI) Summary associated with each new animal anesthetic.

PROPOFOL (NADA 141-070, approved 1996) is an IV injectable anesthetic for induction of anesthesia, for maintenance of anesthesia using intermittent bolus injections, and for induction of anesthesia prior to inhalational maintenance anesthesia.

Effectiveness Study Design for Propofol Injectable

The induction dosage was determined using 30 dogs divided into 3 treatment groups; each group was given a different dose of propofol. Dogs received routine supplemental oxygen when oxygen saturation levels decreased below 90%. Masked induction observations were recorded for:

- time to induction
- time to recovery
- duration of anesthesia
- response to tail clamp
- pulse rate (PR)
- respiratory rate (RR)
- systolic, diastolic & mean arterial blood pressure (BP)
- adverse reactions

A separate study determined the injectable bolus dose of propofol required to maintain anesthesia for 30 minutes in the same 30 dogs. Dogs were induced to anesthesia using the induction dose determined in the previous study. Three different maintenance bolus doses were evaluated. Investigators were not masked to the propofol doses. The same observations from the first study were recorded after each bolus dose.

A third laboratory crossover design study used 36 dogs to evaluate propofol's compatibility and dose-sparing effects when administered concurrently with commonly used preanesthetics, other induction agents (I) and other maintenance anesthetics (M). Maintenance anesthesia continued for 30 minutes. The same observations were recorded. Each of 17 treatment groups contained 6 dogs (Table 1, next page).

The clinical field trial evaluated 325 dogs at private practices or veterinary teaching hospitals. Procedures primarily included ovariohysterectomies, dental cleaning, tumor removal,

(Continued, next page)

TABLE 1.
Laboratory Crossover Design Study Evaluating Propofol Compatibility:
Usage in 17 Treatment Groups

- atropine, propofol
- atropine, medetomidine, propofol
- atropine, propofol (I), propofol (M)
- oxymorphone, propofol
- glycopyrrolate, propofol
- atropine, medetomidine, propofol, atipamezole
- atropine, acepromazine, propofol (I), propofol (M)
- propofol, methoxyflurane
- acepromazine, propofol
- xylazine, propofol
- atropine, medetomidine, propofol (I), propofol (M)
- acepromazine, butorphanol, propofol
- diazepam, propofol
- propofol, isoflurane
- butorphanol, propofol
- propofol, halothane
- atropine, medetomidine, propofol

I = Induction agent M = Maintenance Anesthetics

TABLE 2.
Clinical Field Trial (325 Dogs) Involving Propofol

Anesthetic Regimen	*Number of Dogs*
Propofol Induction and Maintenance	42
Acepromazine/Propofol	47
Oxymorphone/Propofol	48
Xylazine/Propofol	41
Butorphanol/Propofol	24
Acepromazine/Butorphanol/Propofol	24
Propofol/Halothane	51
Propofol/Isoflurane	48
Total Number of Dogs	325

wound repair and radiography. Times and quality of induction, anesthesia and recovery were recorded, as well as physiological parameters (PR, RR, BP), and adverse reactions. Treatment groups are indicated in Table 2.

SAFETY STUDY DESIGN FOR PROPOFOL INJECTABLE

An acute toxicity study determined the margin of safety of a single IV dose of propofol and the progression of clinical signs associated with propofol overdosage. Four healthy beagle dogs were included in each of 3 treatment groups at 3, 4.5, and 6 times the proposed induction dose. Observations of clinical signs and adverse reactions continued for 14 days. Necropsy was done on any animal that died.

The main safety study evaluated the toxicity of repeated IV doses of propofol over a 30-day period. Ten dogs in each of 5 treatment groups were given either saline, the vehicle, or propofol at 0.76, 1.5, or 4.5 times the induction dose. Dogs in the first 4 treatment groups were anesthetized daily. Dogs receiving 4.5 times the propofol induction received 13 anesthetic episodes over the 30-day study.

Observations included physical examinations (PE), body weight (BW), food consumption, recovery time, PR, RR, temperature (T), electrocardiogram (ECG), BP, clinical pathology, urinalysis (UA), gross necropsy, and histopathology.

A separate study examined the tolerance of the cephalic vein wall to the intravenous injection of propofol in four dogs. Each dog received an injection of sterile saline into the right cephalic vein and propofol into the left cephalic vein on three consecutive days. The propofol dose was 1.5 times the induction dose. Injection areas were examined before and 1, 2, and 6 hours after injection on days 1 and 2; as well as before and 1 and 2 hours after injection on day 3. During necropsy on the third day, 8 cm of cephalic vein were removed from each leg. Samples for histology were removed from two sites: 3 and 6 cm proximal to the injection site.

PROPOFOL (NADA 141-098) was approved in 1997 with the same indications.

EFFECTIVENESS STUDY DESIGNS FOR PROPOFOL INJECTABLE

Dosage was evaluated after the passage of the Animal Drug Availability Act. Instead of dosage determination study design, induction and maintenance dosage characterization was based on the results of two pilot studies conducted in dogs.

A clinical field trial evaluated 419 dogs requiring general anesthesia for surgical or nonsurgical procedures. Dogs were assigned to a treatment group according to individual patient needs. Procedures were grouped as surgical/invasive (n = 228), nonsurgical/minimally invasive (n = 113) and diagnostic/noninvasive (n = 78). The most commonly used preanesthetics and anesthetics were evaluated in the presence of propofol induction or maintenance as shown in Table 3 (next page).

Observations included dosages, propofol injection times, induction, anesthesia and recovery times, PR, RR, BP, T, end tidal CO_2, oxsat, use of supplemental O_2 and adverse reactions. Descriptive statistics were used to evaluate data since dogs were not randomly assigned to treatment groups.

SAFETY STUDY DESIGNS USING PROPOFOL INJECTABLE

Acute toxicity was evaluated in 4 dogs. Each anesthetic episode was separated by 4 to 5 days. Induction was initially at the proposed label dose. During each subsequent anesthetic episode, propofol was administered in doses that were incrementally increased until the occurrence of a previously defined serious adverse reaction (for example, apnea > 90 seconds). One additional excessive dose was given. Recovery times, ECG, mucous membrane color, T, RR, BP, and adverse reactions were recorded.

(Continued, next page)

TABLE 3.
Clinical Field Trial (419 Dogs) Involving Propofol:
Usage in 11 Treatment Groups

- propofol (I + M) *n = 49*
- acepromazine, propofol (I + M) *n = 48*
- acepromazine, oxymorphone, propofol (I + M) *n = 16*
- xylazine, butorphanol, propofol (I + M) *n = 16*
- diazepam, butorphanol, propofol (I + M) *n = 16*
- propofol (I), isoflurane (M) *n = 52*
- acepromazine, oxymorphone, propofol (I), isoflurane (M) *n = 54*
- xylazine, butorphanol, propofol (I), isoflurane (M) *n = 46*
- diazepam, oxymorphone, propofol (I), isoflurane (M) *n = 13*
- diazepam, butorphanol, propofol (I), isoflurane (M) *n = 53*
- acepromazine, oxymorphone, propofol (I), isoflurane (M) *n = 56*

I = Induction agent M = Maintenance Anesthetics

In the main safety study, 24 healthy dogs (8 dogs in each of 3 groups) were anesthetized every other day over 11 days. Anesthesia was induced with low doses of propofol (6.5 mg/kg) or high doses (19.5 mg/kg) using a standardized rate of administration. Anesthesia was maintained with 3 or 6 bolus injections of 1.7 mg/kg propofol. A third group of dogs was injected with saline at a volume equal to that of the high dose. Parameters included PE, BW, food consumption, RR, T, lung auscultation, mucous membrane color, clinical pathology, recovery times, and adverse reactions. Physiologic responses were measured before and at specified times during each anesthetic episode. All dogs were necropsied on day 13 of the study.

SEVOFLURANE (NADA 141-103), an inhalational anesthetic, was approved in 1999 for induction and maintenance of general anesthesia in dogs.

EFFECTIVENESS STUDY DESIGNS FOR SEVOFLURANE

Dosage was characterized using 40 dogs by establishing MAC (minimal alveolar concentration) for sevoflurane, isoflurane, and halothane. Anesthesia was induced by mask or sealed chamber using 5% sevoflurane (18 dogs), 4% isoflurane (10 dogs), or 4% halothane (12 dogs). Dogs were intubated and ventilation was controlled. A predetermined end tidal anesthetic concentration was maintained for 20-40 minutes and then the dog's tail was clamped. The concentration midway between the highest concentration that allowed purposeful movement and the lowest concentration that prevented purposeful movement was taken as 1 MAC.

Dosage was further characterized using 16 dogs in a sevoflurane/isoflurane crossover study. Anesthesia was induced by increasing the vaporizer delivered concentration (VDC) at 15 second intervals from 0.5 to 2.0 MAC in increments of 0.5 MAC. The setting of 2.0 MAC was maintained until endotracheal intubation was accomplished. Dogs breathed spontaneously at an oxygen flow of 1 L/minute for 30 minutes of maintenance anesthesia. The vaporizer was then turned to 0% and oxygen was increased to 4 L/minute until the dog was extubated. A positive response to the tail clamp, applied at 1 minute intervals during recovery, was used to indicate the end of anesthesia. Vaporizer settings, inspired and expired anesthetic concentrations, induction and recovery times were recorded throughout anesthesia. Quality of induction and recovery were assessed. PR, RR, oxsat, BP and T were recorded throughout the anesthetic period.

Compatibility with injectable induction and preanesthetic drugs was evaluated in two laboratory studies (8 dogs in each study). Both studies were represented by four treatment groups in two 4 X 4 Latin Square arrangements. The treatment groups for each study are listed in the following Tables 4 and 5 (next page).

Sevoflurane concentration and measurement of inspired and expired sevoflurane were measured throughout anesthesia. Dose sparing effects of preanesthetics on induction and maintenance were determined. Induction and recovery times, RR, BP, PR, T, oxsat, ECG, and expired CO_2 were recorded throughout anesthesia. Adverse reactions were recorded by treatment group and phase of anesthesia. Descriptive statistics were used to evaluate the concurrent use of premedications and induction agents with sevoflurane.

The clinical field trial evaluated 196 dogs at 3 sites. Surgical and non-surgical procedures of various duration and complexity were performed. Health status and type of procedure were used to determine the most appropriate anesthetic regimen (non-randomized).

All dogs breathed spontaneously during anesthesia and the use of an anticholinergic was optional for all of the treatment groups noted in Table 6.

(Continued, next page)

TABLE 4.
Compatibility Study 1 (8 Dogs)
– Four Treatment Groups –

Preanesthetic	*Induction*	*Maintenance*
• none	sevoflurane	sevoflurane
• none	thiopental	sevoflurane
• none	propofol	sevoflurane
• none	ketamine/diazepam	sevoflurane

TABLE 5.
Compatibility Study 2 (8 Dogs)
– Four Treatment Groups –

Preanesthetic	*Induction*	*Maintenance*
• acepromazine	thiopental	sevoflurane
• xylazine	thiopental	sevoflurane
• butorphanol/acepromazine	thiopental	sevoflurane
• oxymorphone/acepromazine	thiopental	sevoflurane

Study parameters included vaporizer concentrations and flow rates, induction and recovery times, quality of induction, maintenance and recovery, RR, BP, PR, T, oxsat, ECG, and expired CO_2. Incidence and duration of adverse reactions recorded by treatment group and phase of anesthesia. Descriptive statistics were used to evaluate the concurrent use of premedications and induction agents with sevoflurane.

SAFETY STUDY DESIGNS FOR SEVOFLURANE

Acute toxicity was evaluated in 23 dogs divided and anesthetized twice (once with sevoflurane and once with halothane) for one hour. The effects of various concentrations of sevoflurane and halothane on pulse rate and blood pressure were recorded. Adverse reactions were recorded.

The main safety study was conducted in 16 dogs (8 dogs received sevoflurane; 8 halothane) evaluated during ten 3-hour periods of anesthesia over 2 weeks (3 hours/day, 5 days per week). After masked induction, four dogs in each group breathed spontaneously and four were ventilated. The study evaluated arrhythmogenic potential during the 10th anesthetic episode. All dogs were necropsied. Observations included PE, food consumption, BW, induction and recovery times. During the 1st and 10th exposures, BP was recorded every 15 minutes, arterial blood gases every 30 minutes. RR, ECG, EEG, and T were monitored continuously. Clinical pathology blood samples were taken before the study and just before the 10th anesthetic episode. Urine was sampled and a liver biopsy was performed before the 1st anesthetic episode and at necropsy.

A different study evaluated hepatotoxicity. Twelve dogs were divided into three groups and given sevoflurane, halothane, or enflurane for 1 hour. BP was measured before anesthesia, at 30 minutes, at the end of anesthesia and at 1, 2 and 3 hours post exposure. Clinical pathology samples were taken before anesthesia, immediately after anesthesia, and at 3, 6, 8, 10, 12, 24, 48, and 72 hours post exposure. Necropsy was performed at 72 hours to evaluate gross lesions, liver weights and liver histopathology.

TABLE 6.
Clinical Field Trial (196 Dogs)
– Six Treatment Groups –

Preanesthetic	*Induction Drug*	*Number of Dogs*
• oxymorphone	thiopental	39
• acepromazine/ oxymorphone	thiopental	30
• butorphanol/ xylazine	thiopental	29
• opioid	propofol	33
• optional*	sevoflurane	30
• optional*	optional*	35

* Results from optional treatment groups were difficult to evaluate and would not be recommended for inclusion in future anesthetic clinical trials.

Fluoride ion production and elimination was evaluated in 4 dogs. Dogs were anesthetized for 3 hours in conditions that maximized the production of fluoride ions. Twenty-four hour samples of blood, urine and feces were taken at 1, 2, 7, and 14 days after anesthesia and were evaluated for inorganic fluoride. Clinical pathology, induction and recovery times were evaluated. RR, PR, BP and blood gases were monitored during anesthesia. The entire study was then repeated at a higher sevoflurane concentration and samples were collected for 7 days post exposure. One month later the dogs were necropsied.

NOTE: In addition to effectiveness and safety studies described above, all anesthetics addressed several important related issues prior to approval including: arrhythmogenicity, effects in sighthounds, human safety, and human abuse potential.

References

1. Freedom of Information Summary for NADA 141-070, Propofol for Dogs and Cats, Schering-Plough Animal Health, Inc.
2. Freedom of Information Summary for NADA 141-098, Propofol for Dogs, Abbott Laboratories, Inc.
3. Freedom of Information Summary for NADA 141-103, Sevoflurane, Abbott Laboratories, Inc.

NOTE: Freedom of Information Summaries are available on the CVM Home Page at *www.fda.gov/cvm.*

Dr. Connolly is the anesthetics reviewer in CVM's Division of Therapeutic Drugs for Non-Food Animals.

□

8 PET FOOD: THE LOWDOWN ON LABELS

by Linda Bren

This article appeared in the May/June 2001 issue of the ***FDA Consumer****.*

Choosing a pet food from among the cans, bags, and boxes stacked on store shelves can be a daunting experience. Which formulation of food is best? Is my dog old enough for "adult formula"? Does my cat really need "premium"? Will Fido be healthier on "natural" food and will Fluffy fully appreciate "gourmet"?

U.S. consumers spend more than $11 billion a year on cat and dog food, according to the Pet Food Institute. And pet food manufacturers compete for these dollars by trying to make their products stand out among the many types of dry, moist, and semi-moist foods available. Pet food packaging carries such descriptive words as "senior," "premium," "super-premium," "gourmet," and "natural." These terms, however, have no standard definition or regulatory meaning.

But other terms do have specific meanings, and pet foods, which are regulated by the Food and Drug Administration's Center for Veterinary Medicine (CVM), must carry certain information on their labels. Consumers can be confident that their pets are eating a nutritionally sound food if they understand the full significance of these labels.

The Right Stuff: Choosing a Good Pet Food

So how can pet owners choose the right food for their pets? CVM's pet food specialist William Burkholder, D.V.M., Ph.D., recommends examining three parts of the pet food label: the life stage claim, the contact information for the manufacturer, and the list of ingredients.

Pet owners should look for the word "feeding" in the life stage claim (found in the nutritional adequacy statement on the label). This means the food was proven nutritionally adequate in animal feed tests.

Another item to check on the label is the contact information. Pet owners should look for the manufacturer's telephone number. Only the manufacturer's name and address are required, but people should be able to call manufacturers to ask questions about their products, says Burkholder, and manufacturers should be responsive. "They will not tell you how much liver, for example, is in their product, because that's part of their proprietary formula. But they should tell you how much of any nutrient is in the product."

The ingredients list on the label is an area of consumer preference and subjectivity. Pet owners who do or do not want to feed a pet a certain ingredient can look at the list of ingredients to make sure that particular substance is included or excluded.

Some people prefer to pass up animal by-products, which are proteins that have not been heat processed (unrendered) and may contain heads, feet, viscera and other animal parts not particularly appetizing. But protein quality of by-products sometimes is better than that from muscle meat, says Burkholder.

"Meal" is another ingredient that some people like to avoid. In processing meat meal or poultry by-product meal, by-products are rendered (heat processed), which removes the fat and water from the product. Meat or poultry by-product meal contains parts of animals not normally eaten by people.

Some consumers try to avoid pet foods with synthetic preservatives, such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and ethoxyquin. Ethoxyquin, in particular, has been hotly debated. Current scientific data suggest that ethoxyquin is safe, but some pet owners avoid this additive because of a suspected link to liver damage and other health problems in dogs. CVM has asked pet food producers to voluntarily lower their maximum level of ethoxyquin in dog food while more studies are being conducted on this preservative, and the industry is cooperating.

Many products preserved with naturally occurring compounds, such as tocopherols (vitamin E) or vitamin C, are available. These products have a much shorter shelf life than those with synthetic preservatives, especially once a bag of food is opened.

Some animal nutritionists recommend switching among two or three different pet food products every few months. Burkholder says nutritional advice for people to eat a wide variety of foods also applies to pets.

(Continued, next page)

Doing so helps ensure that a deficiency doesn't develop for some as yet unknown nutrient required for good health. When changing pet foods, add the new food to the old gradually for a few days to avoid upsetting the pet's digestive system.

Pet Food Safety and Nutrition

No matter what choice they make, consumers can take comfort in knowing that pet food is manufactured under a series of standards and regulations. These regulations require some nutrients and additives, disallow others, and stipulate certain information that must be on the label. The labels of packages and cans of commercial cat and dog food must list five pieces of information: guaranteed analysis, nutritional adequacy statement, ingredients, feeding guidelines, and the manufacturer's name and address.

With the exception of a nutritional adequacy statement, these items must also appear on commercial food labels for other pets, such as gerbils, snakes, and parakeets.

Guaranteed Analysis

The guaranteed analysis specifies the product's minimum percentages of crude protein and crude fat. It also gives the maximum percentages of crude fiber and moisture. ("Crude" refers to a specific method of measuring the nutrient, and is not an indication of quality.) Although not required, some manufacturers also specify the percentages of other nutrients, such as ash and taurine in cat food, and calcium and phosphorus in dog food.

The amounts of crude protein and most other nutrients appear less for canned products than for dry ones because of differences in moisture content. Canned foods typically contain about 75 percent water, while dry foods contain only about 10 percent.

Nutritional Adequacy

The nutritional adequacy statement assures consumers that a product meets all of a pet's nutritional needs. The Association of American Feed Control Officials (AAFCO), an advisory body of state and federal feed regulators, develops recommended standards for nutrient contents of dog and cat foods. AAFCO also publishes ingredient definitions and regulations.

The FDA's CVM works in partnership with AAFCO to determine safe pet food ingredients and testing protocols. In addition to federal regulation of pet food, most state governments regulate pet foods and labeling through their agricultural departments. AAFCO has created a model feed bill that states often adopt in their own laws.

CVM gives scientific and regulatory advice to AAFCO and the states on pet food issues, and CVM representatives serve on AAFCO committees and meet regularly with AAFCO's board of directors. CVM investigators also team with AAFCO to check out questionable pet food ingredients or claims.

Manufacturers can show their food meets AAFCO's standards for nutritional adequacy by calculations or by feeding trials. Calculations estimate the amount of nutrients in a pet food either on the basis of average nutrient content of its ingredients, or on results of laboratory tests—but not animal feed tests. If the calculations show that the food provides sufficient nutrients to meet the specific AAFCO nutritional profile referenced, the pet food label will carry a statement like: "(Name of product) is formulated to meet the nutritional levels established by the AAFCO (Dog or Cat) Food Nutrient Profiles for (specific life stage)."

Feeding trials signify that the manufacturer has tested the product (or a similar product made by the same manufacturer) in dogs or cats under strict guidelines. Products found to provide proper nutrition based on feeding trials will carry a statement such as: "Animal feeding tests using AAFCO procedures substantiate that (name of product) provides complete and balanced nutrition for (specific life stage)."

Photo by Sharon Benz

Regardless of the method used, the nutritional adequacy statement on a cat or dog food label must also tell which life stage the product is suitable for. AAFCO has established two nutrient profiles each for dogs and cats—growth/lactation and maintenance—to fit their life stages.

Every product must meet at least one of these two profiles. A product intended for growing kittens and puppies, or for pregnant or lactating females, must meet AAFCO's nutrient profile for growth/lactation. Products that meet AAFCO's profile for maintenance are suitable for an adult, non-reproducing dog or cat of normal activity level, but may not be adequate for an immature, reproducing, or hard-working animal. A product may claim that it is for "all life stages" if it is suitable for adult maintenance and also meets the more stringent nutritional needs for growth and reproduction.

Growth/lactation and maintenance are the only nutrient profiles authorized by AAFCO and CVM, so terms like "senior" or "formulated for large breed adults" mean the food meets the requirements for adult maintenance—and nothing more.

Snacks and treats that are clearly identified as such are not required to include a nutritional adequacy statement. But these foods, in all other respects, must meet FDA and state regulations for pet food labeling. Dog chews made from rawhide, bone, or other animal parts (such as pig ears) are also considered "food" since pets eat them. These products must bear a list of ingredients and provide the manufacturer's name and address, but they are not required to

(Continued, next page)

Photo by Sharon Benz

give a guaranteed analysis, nutritional adequacy statement, or feeding instructions.

Ingredients

Like human foods, pet foods are regulated under the Federal Food, Drug, and Cosmetic Act, and must be pure and wholesome, and contain no harmful substances. They also must be truthfully labeled. Foods for human or pet consumption do not require FDA approval before they are marketed, but they must be made with ingredients that are "generally recognized as safe" (GRAS) or ingredients that are approved food and color additives. If scientific data show that an ingredient or additive presents a health risk to animals, CVM can prohibit or modify its use in pet food.

Pet food ingredients must be listed on the label in descending order by weight. However, the weight includes the moisture in the ingredient, which makes it tricky to interpret. "A moist ingredient, such as chicken, which may be 70 percent water, may be listed ahead of a dry ingredient, such as soybean meal, which is only 10 percent water—yet the soy actually contributes more solids to the diet," says Susan Donoghue, V.M.D., owner of Nutrition Support Services, Inc., and past president of the American Academy of Veterinary Nutrition.

Similar materials listed as separate ingredients may outweigh other ingredients that precede them on the list of ingredients. For example, chicken may be listed as the first ingredient, then wheat flour, ground wheat, and wheat middlings. The consumer may believe that chicken is the predominant ingredient, but the three wheat products—when added together—may weigh more than the chicken.

Dietary Supplements

Just as dietary supplements for people are growing in popularity, so are animal food supplements for pets. "Many people treat their dogs and cats like replacement children," says Jennifer Kvamme, D.V.M., associate editor of Petfood Industry magazine. "They want the best for them, and want to give them the types of food and supplements that they would eat themselves."

The FDA considers animal food supplements that are not approved nutrients or GRAS to be unapproved food additives or unapproved new animal drugs. As such, they are not permitted in pet food. Nevertheless, consumers will see on some cat and dog food labels ingredients such as glucosamine and chondroitin, which are claimed to alleviate joint stiffness and pain, and St. John's wort, purported to treat depression and relieve stress.

Neither the FDA nor state feed control officials have the number of employees required to monitor every supplement and food manufacturer and prevent those using unapproved ingredients from selling their products, says Burkholder. "It's a matter of profit incentive versus likelihood of getting caught. The same forces apply for why police cannot write speeding tickets to everyone driving over the speed limit. That doesn't make speeding legal."

Burkholder cautions people to check with their veterinarians before giving their pets supplements, whether alone or in a food product. "Many persons do not appreciate that dogs and cats are not small furry people. They often think that a supplement that they may take themselves is good for their pet, but that may not be the case."

Table Scraps May Be Dangerous

Some people think a food that they eat is good for their pets. Not true. Some human foods, in fact, may be dangerous to pets. "Most pet owners simply do not know that small amounts of chocolate, onions, macadamia nuts and bread dough can be fatal if ingested by a dog," says Steve Hansen, D.V.M., senior vice president of the ASPCA Animal Poison Control Center. "And cats, in particular, have a body chemistry quite different from ours," and so are susceptible to poisoning from a number of human foods. Also because of their different body chemistry and nutritional requirements, cats should not be fed dog food, says Burkholder.

Feeding Guidelines

Feeding directions on pet food provide only a broad guideline. Nutritional requirements vary according to a pet's age, breed, body weight, genetics, amount of activity, and even the climate in which the pet lives.

Many owners are guilty of overfeeding their pets, and even a "light" food can cause weight gain if fed in excess of caloric needs. "It's estimated that about 25 percent of dogs and cats that enter a pet clinic are overweight," says Burkholder. Obesity can shorten a pet's life by contributing to heart and liver problems, diabetes, arthritis, bladder cancer, and skin disorders and it can put a pet at higher risk while undergoing anesthesia and surgery. Pet owners should consult their veterinarians for the appropriate amount and type of food to give their pets, especially those that are overweight.

A pet food can claim to be "light" or "lean" only if it meets AAFCO's standard definitions for these terms. These definitions differ for dog and cat food and also depend on the moisture content of the food. The words "light," "lite" and "low calorie" all have the same meaning.

The words "lean" and "low fat" also mean the same. But "less calories" and "reduced calories" mean only that the product has fewer calories than another product, and "less fat" and "reduced fat" mean the product is less fatty than another

(Continued, next page)

one. In both cases, the manufacturer must state on the label the percentage of reduction and the product of comparison.

Most pet food labels do not provide calorie content, but consumers can get this information by contacting the manufacturer, whose location must be on the label. Many manufacturers provide a toll-free number for consumers as well as their Web site address.

When a 'Food' is a 'Drug'

Statements that a product can treat, prevent or reduce the risk of a disease are considered drug claims and are not allowed on pet food. CVM also disallows claims such as "improves skin and coat," "prevents dry skin," and "hypoallergenic." Consumers may see phrases such as "promotes healthy skin" and "promotes glossy coat." CVM permits these claims, but any healthy animal that gets adequate nutrition should have these qualities anyway without eating a special food.

Recognizing the close link between diet and disease, CVM does allow certain health-related information on labels to help consumers evaluate pet foods. For example, while a product cannot claim to treat feline lower urinary tract disease, a concern for some cat owners, it may make the claim that the food "reduces urine pH to help maintain urinary tract health," provided data generated by the manufacturer and reviewed by CVM support the statement.

CVM permits some dental claims on pet foods. The jaw movement of animals as they chew on certain foods or treats, or some chemicals in foods, can help reduce plaque and tartar, so CVM allows claims such as "helps control plaque" and "helps control tartar." CVM does not allow claims to treat or prevent gingivitis or periodontal disease because these are drug claims.

Pet owners may see claims such as "improves doggie breath" on pet food or treats. These claims have no regulatory meaning; manufacturers

Keeping Pet Food Fresh

Always keep canned pet food refrigerated after opening.

If you store dry pet food in a container other than its original bag, be sure to wash the empty container with soap and water before adding food from a new bag. The residual fat that settles on the bottom of the container can become rancid beyond its shelf life (the date stamped on the bag). This spoiled fat may contaminate fresh food added to the container, causing vomiting or diarrhea when fed to your pet.

—L.B.

Irradiation of Pet Food

In April, the FDA approved an irradiation process that can be used on all animal feed and feed ingredients, including pet food and treats. This process can reduce the risk of contamination from all strains of Salmonella bacteria. Salmonella organisms can cause gastrointestinal upset and diarrhea in people and pets.

Irradiation, which causes chemical changes, is already approved for use on a variety of human foods. Extending this process to pet and other animal foods will increase the safety of the food for both the animals consuming it and the people handling it.

—L.B.

Pet Food and the Risk of 'Mad Cow Disease'

No evidence of bovine spongiform encephalopathy (BSE), commonly known as "Mad Cow Disease," ever has been detected in horses, dogs, and other pets, such as birds, reptiles, and gerbils. However, a feline version of BSE, first identified in 1989, has been documented in domestic cats in Europe, mostly in the United Kingdom, according to the U.K.'s Ministry of Agriculture, Fisheries and Food.

No cases of BSE or similar forms of the disease in cats, cows, or humans ever have been found in the United States. "The same precautions that the U.S. government is taking to keep BSE out of this country's cattle are also protecting our pets," says William Burkholder, D.V.M., Ph.D., the FDA's pet food specialist.

Scientists believe BSE is transmitted through animal feed containing certain animal proteins that may harbor the BSE agent. Since 1991, the United States has banned the import of animal foods, including pet food, containing ruminant (such as cattle or sheep) materials from countries with BSE. In 1997, the United States extended the ban to most of Europe.

In December 2000, the U.S. banned imports of animal proteins—from any species—from 31 countries that either are known to have BSE in their cattle herds or are considered at high risk for having it. This means that no meat-containing pet food can legally be imported from a country at risk for BSE.

—L.B.

use them simply to promote their products.

The phrase "recommended by veterinarians" also has no regulatory meaning, says Rodney Noel, Ph.D., AAFCO's pet food committee chair and a chemist at Purdue University. "There is no minimum number or percentage of veterinarians required for a company to be able to state its product is recommended by vets," Noel says.

CVM provides manufacturers some latitude in making health claims regarding a category of food known as veterinary medical foods, which consumers can obtain only through a veterinarian. Manufacturers design these foods to treat a particular disease or condition. Although not regulated as drugs, these foods may carry health information in promotional materials for the veterinarian to help them treat their patients correctly.

Making Sense of 'Light' and 'Lean' in Pet Food

The calorie and fat contents listed below are the maximum limits allowed in dog and cat food labeled "light" or "lean." These definitions are established by the Association of American Feed Control Officials and authorized by the FDA. Comparisons between products in different categories of moisture content are considered misleading.

	Dry Foods (< 20 % water)	*Semi-moist Foods (20–65 % water)*	*Moist Foods (> 65 % water)*
Light, Lite or Low Calorie	Dogs: 1,409 calories per pound Cats: 1,477 calories per pound	Dogs: 1,409 calories per pound Cats: 1,477 calories per pound	Dogs: 409 calories per pound Cats: 432 calories per pound
Lean or Low Fat	Dogs: 9 percent fat Cats: 10 percent fat	Dogs: 7 percent fat Cats: 8 percent fat	Dogs: 4 percent fat Cats: 5 percent fat

For additional regulatory information on pet food and labeling, call CVM at 301-594-1755 or visit www.fda.gov/cvm.

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

□

APPROVAL WITHDRAWN FOR ABBOTT LABORATORIES' POULTRY FLUOROQUINOLONE DRUGS

Effective April 30, 2001, FDA's Center for Veterinary Medicine (CVM) withdrew the approvals of two new animal drug applications (NADAs) sponsored by Abbott Laboratories. The NADAs provide for use of sarafloxacin antimicrobial drugs to treat poultry. One is NADA 141-017 for SaraFlox® (sarafloxacin hydrochloride) WSP, a water-soluble powder used in the drinking water of broiler chickens and growing turkeys for control of mortality associated with *Escherichia coli*. The other is NADA 141-018 for SaraFlox® (sarafloxacin hydrochloride) Injection; an injectable solution used in 18-day embryonated broiler eggs and day-old broiler chickens for control of early chick mortality associated with *E. coli*.

Last year, CVM informed Abbott Laboratories that, on the basis of new data and information before it, there is a question of human food safety—the potential for the development of resistant organisms—due to the use of fluoroquinolones such as sarafloxacin in poultry. Specifically, that CVM has determined that:

- The use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter*, a pathogen to humans, in poultry;
- This fluoroquinolone-resistant *Campylobacter* is transferred to humans and is a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans; and
- Fluoroquinolone-resistant *Campylobacter* infections are a hazard to human health.

Fluoroquinolones also are approved for use in humans, and they are considered to be one of the most valuable antimicrobial drug classes available to treat human infections because of their spectrum of activity, safety, and ease of administration. This class of drugs is effective against a wide range of human diseases and is used both in treatment and prophylaxis of bacterial infections in the community and in hospitals. Fluoroquinolones are used routinely by physicians for the treatment of foodborne disease. These diseases have a major public health consequence in the United States. After being informed by CVM of this human food safety question, Abbott Laboratories requested voluntary withdrawal of approval of NADAs 141-017 and 141-018.

Additional information about this withdrawal is available in the April 30, 2001, *Federal Register (http://www.fda.gov/OHRMS/DOCKETS/98fr/043001h.htm*), and from Dr. Mohammad I. Sharar, Center for Veterinary Medicine (HFV-216), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-0159. Information about CVM's concern about antimicrobial resistance may be found on the CVM Home Page at: *http://www.fda.gov/cvm/antimicrobial/antimicrobial.html*.

□

PATHOGEN LOAD REPORT AVAILABLE

FDA's Center for Veterinary Medicine (CVM) contracted with Exponent of Alexandria, Virginia to conduct a review of published literature on the effect of using antimicrobials in food-producing animals on pathogen load. This review has been completed, and the report is available on the CVM Home Page (*http://www.fda.gov/cvm/antimicrobial/antimicrobial.html*). Requests for paper copies of this document may be submitted to the *FDA Veterinarian*.

In November 1998, FDA's CVM published in the *Federal Register* a notice of availability for the draft guidance document entitled "Consideration of the Human Health Impact of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals" (Guidance for Industry #78). In this guidance document (*http://www.fda.gov/cvm/guidance/guidad78.html*), CVM stated that the Agency intended to consider the potential human health impact of the microbial effects associated with all uses of all classes of antimicrobial new animal drugs intended for use in food-producing animals. The guidance said that in order to assess this impact, it may be necessary to evaluate the following two separate, but related aspects: 1) the rate and extent of development of antimicrobial drug resistant enteric bacteria formed in the animal's intestinal tract following exposure to the antimicrobial new animal drug (resistance); and 2) changes in the number of enteric bacteria in the animal's intestinal tract that cause human illness (pathogen load).

On February 22-24, 2000, CVM held a public scientific meeting on pre-approval studies in antimicrobial resistance and pathogen load. The purpose of this workshop was to discuss the appropriate designs for pre-approval studies to evaluate the potential microbial effects associated with the use of antimicrobial drugs in food-producing animals. The slide presentations from this meeting as well as the complete transcripts are available on the CVM Home Page (*http://www.fda.gov/cvm/antimicrobial/oldmeet.htm*). At the February 2000, meeting, CVM received numerous comments questioning the relevance of conducting studies to try to assess the impact of drug effects on pathogen load.

CVM recognizes that scientific information in this area is limited and acknowledges the concerns raised at the February 2000 public meeting. Therefore, in an attempt to gather additional information on the topic, CVM contracted with Exponent to conduct this literature review entitled "Effect of the use of antimicrobials in food-producing animals on pathogen load: Systematic review of the published literature."

This report represents just one component of CVM's ongoing effort to complete a thorough review of the pathogen load issue and to develop appropriate policy in this area. CVM is planning to seek further scientific input on this issue and will announce its intentions in the near future. Additional comments on the pathogen load issue or comments on the report may be submitted to FDA's Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD, 20852; or faxed to (301) 827-6870. Please refer to Docket No. 98D-0969 in your submission.

Further information on the report is available from Dr. William T. Flynn, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 301-827-4514, e-mail at *wflynn@cvm.fda.gov <mailto:wflynn@cvm.fda.gov>*.

□

REGULATORY ACTIVITIES

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

- Joe A. Meneses, Partner, Areias & Meneses Dairy, Fresno, CA
- Carlyn A. Jensen, Owner, Jensen Dairy, Hanford, CA
- E. Manuel Costa, Owner, C & C Holsteins, Hanford, CA

These violations involved illegal residues of penicillin in dairy cows. Follow-up inspections revealed lack of adequate systems for determining the medication status of animals offered for slaughter, for assuring that medicated animals have been withheld from slaughter for appropriate periods of time to deplete hazardous residues of drugs, for assuring that drugs are used in a manner consistent with the directions contained in their labeling, and for determining the quantities of drugs used to medicate animals. In addition, Mr. Meneses was found to be adulterating the drug Agri-Cillin brand Penicillin G Procaine Injectable Suspension, by administering one 40 ml injection per day at one site, resulting in an overdose, and likely causing the illegal residues found in the animal consigned for slaughter.

Mr. Jensen was found to be adulterating the drug Pfi-Pen G by administering one 50 ml injection per day at one site. He also used Tylan 200, which is not approved for use in lactating dairy cattle.

Mr. Costa was found to be adulterating the drug Agri-Cillin by administering a mixture of 30 ml of water with 30 ml of Agri-Cillin to prepare a uterine infusion to medicate his lactating cattle. In addition, Mr. Costa

(Continued, next page)

has a history of offering five (5) animals for sale for human food which have been found to be adulterated with drug residues between 1993 and 1996.

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).

- Matt Geib, Owner, Greeley Elevator Company, Greeley, CO
- Brian J. Raymond, Owner, Sandy Lake Mills, Sandy Lake, PA
- Eugene P. Yachere, Owner, Yachere Feed, Rockwood, PA
- Michael Bensman, President, Minster Farmers Cooperative Exchange, Inc., Minster, OH
- Richard A. Warren, Manager, Perry Coal and Feed Co., Perry, OH
- Alan R. Beckwith, General Manager, Jefferson Milling Co., Jefferson, OH
- Gary E. Berrier, Owner, Dorset Milling, Dorset, OH
- Jeffrey Ettinger, President, Earl B. Olson Feed Mill, Willmar, MN
- James A. Bose, President, Lime Creek Ag Services, Inc., Fulda, MN
- Kenneth H. Sherwood, President, Alaska Garden and Pet Supply, Inc., Anchorage, AK
- Dale L. Danielson, Manager, Adrian Elevator, Inc., Butterfield, MN
- Jerry M. Behimer, President, Material Resources, LLC – Gateway Co-Packing Company, Washington Park, IL
- Dr. F. Abel Ponce de Leon, Chair, Department of Animal Science, University of Minnesota, St. Paul, MN
- Robert E. Rahrig, General Manager, Countryline Co-Op, Inc., Pemberville, OH
- Reid Kooch, President, Wallowa County Grain Growers, Inc., Enterprise, OR
- Karl T. Kule, Co-Owner, Valley Feed Mill, Inc., Orwell, OH
- Thomas Bostic, General Manager, Central Ohio Farmers Cooperative, Inc., Marion, OH

Violations included lack of written procedures for clean-out of the feed mixer; lack of records sufficient to track materials containing meat and bone meal throughout their receipt, processing, and distribution; failure to label feeds which contain, or may contain, prohibited materials with the required cautionary statement "Do Not Feed to Cattle or Other Ruminants;" the unacceptable practice of flushing the mixer with cracked corn that is fed to wild game including deer, a ruminant animal; and, failure to provide measures to avoid commingling and cross-contamination of feeds containing prohibited materials with feeds containing no prohibited materials.

Mr. Gerald Bookey, Owner and Chief Executive Officer, National Foods Corporation, Shoreline, WA, received a warning letter for significant deviations from the Current Good Manufacturing Practice Regulations (GMP's). Violations included failure to prepare and maintain a receipt record for each lot of drug received; failure to maintain a daily inventory record for each drug used, failure to perform a periodic assay of medicated feeds for drug components; failure to have adequate clean-out procedures for all equipment in the manufacture and distribution of medicated feeds; failure to have a Master Record File; and, failure to retain the original production record for not less than one year.

Mr. Glenn D. Baird, President, Classic Care Products, Inc., Chattanooga, TN, received a warning letter for GMP deviations including no component testing, no master production records, incomplete batch production records, failure to conduct stability studies on finished products, no label controls, no cleaning and maintenance records for manufacturing equipment, and failure to follow Standard Operating Procedures. In addition, veterinary drug products manufactured by the firm were misbranded under Section 502(o) of the Federal Food, Drug, and Cosmetic Act, since the firm was not registered, and the veterinary products had not been listed.

Mr. Everett B. Hughes, President and CEO, Veterinary Laboratories, Inc., Lenexa, KS, received a warning letter as a result of GMP deviations including failure to establish and/or follow adequate procedures to control microbiological contamination in products purporting to be sterile; failure to perform adequate investigations on lots of aseptically filled products that were out of established sterility specifications during initial testing; failure to establish adequate procedures detailing out-of-specification investigations with reference to laboratory procedures; and, failure to have adequate complaint procedures established in that instructions concerning FDA post-marketing adverse drug experiences do not describe what needs to be reported or establish timeframes for reporting.

Mr. Robert D. DeGregorio, President, Land O'Lakes Farmland Feed, LLC, Arden Hills, MN, received a warning letter for violations in the feed mill operation located in Dodge City, KS. Deviations included failure to maintain equipment in such a manner as to prevent cross-contamination of medicated feeds; failure to have an adequate clean-out procedure to prevent unsafe contamination; failure to perform the required testing of medicated feeds containing Category II medicated articles; failure to insure that appropriate and accurate labeling is used; and, failure of the Master Files to contain mixing times for medicated feeds.

□

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 141-156)	Amprolium (Amprol), Bacitracin Methylene Disalicylate (BMD®)	Chickens. For the development of active immunity to coccidiosis, increased rate of weight gain, and improved feed efficiency.	**MEDICATED FEED**—The NADA provides for the use of approved, single-ingredient amprolium and bacitracin methylene disalicylate Type A medicated articles to make combination Type C medicated feeds. *Federal Register* 04/19/01
Alpharma, Inc. (NADA 141-142)	Amprolium (Amprol), Bacitracin Methylene Disalicylate (BMD®), Roxarsone (3-Nitro®)	Chickens. For the development of active immunity to coccidiosis, as an aid in the control of necrotic enteritis caused or complicated by *Clostridium spp*. or other organisms susceptible to bacitracin, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation.	**MEDICATED FEED**—The NADA provides for use of approved, single-ingredient amprolium, bacitracin methylene disalicylate, and roxarsone Type A medicated articles to make three-way combination drug Type C medicated feeds. *Federal Register* 04/23/01
Elanco Animal Health Division of Eli Lilly & Co. (NADA 141-172)	Ractopamine hydrochloride (Paylean®), Tylosin (Tylan®)	Swine. Used for increased rate of weight gain, improved feed efficiency, increased carcass leanness, and for prevention and/or control of porcine proliferative enteropathies (ileitis).	**MEDICATED FEED**—The NADA provides for use of ractopamine and tylosin single-ingredient Type A medicated articles to make combination drug Type C medicated feeds. *Federal Register* 04/30/01
Elanco Animal Health Division of Eli Lilly & Co. (NADA 140-942)	Narasin/Nicarbazin (Maxiban®), Bambermycins (Flavomycin®)	Chickens. For prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	**MEDICATED FEED**—The NADA provides for use of approved narasin/nicarbazin and bambermycins Type A medicated articles to make three-way combination Type C medicated feeds. The medicated feeds are used for prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix, E. acervulina, E. brunetti,* and *E.mivati*, and for increased rate of weight gain and improved feed efficiency. Do not feed to laying hens or allow adult turkeys, horses or other equines access to formulations containing narasin. Withdraw 5 days before slaughter. *Federal Register* 05/16/01
Alpharma, Inc. (NADA 141-083)	Lasalocid (Avatec®), Bacitracin Zinc (Baciferm®)	Chickens. For prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	**MEDICATED FEED**—The NADA provides for use of approved lasalocid and bacitracin zinc Type A medicated articles to make two-way combination drug Type C medicated feeds for prevention of coccidiosis caused by *Eimera tenella*, *E. necatrix, E. acervulina, E. brunetti*, *E. mivati*, and *E. maxima*, and for increased rate of weight gain and improved feed efficiency. *Federal Register* 05/29/01 □

SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 96-298)	Lasalocid (Avatec®)	Chickens, Turkeys. For prevention of coccidiosis.	**MEDICATED FEED**—The supplement provides for establishing tolerances for residues of lasalocid in edible tissues of chickens and turkeys. In addition, the acceptable daily intake (ADI) is codified and a tolerance is established for residues of lasalocid in sheep liver. *Federal Register* 04/18/01
Alpharma, Inc. (130-435)	Oxytetracycline hydrochloride (Oxytet)	Turkeys, Swine. For treatment of various bacterial diseases of livestock.	**ORAL**—The supplement provides for a revised withdrawal time for use of oxytetracycline hydrochloride soluble powder in the drinking water. The NADA provides for a zero-day slaughter withdrawal time. *Federal Register* 04/30/01
Pharmacia and Upjohn Co. (NADA 140-338)	Ceftiofur sodium (Naxcel®) Rx	Goats. For treatment of goat pneumonia.	**INTRAMUSCULAR**—The supplement provides for use of Naxcel sterile powder for injection for treatment of caprine respiratory disease associated with *Pasteurella haemolytica* and *P. multocida*. *Federal Register* 04/30/01
Elanco Animal Health Division of Eli Lilly & Co. (NADA 118-980)	Narasin (Monteban®)	Chickens. For the prevention of coccidiosis.	**MEDICATED FEED**—The supplement provides for establishing a tolerance for residues of narasin in the abdominal fat of chickens and for codifying the acceptable daily intake (ADI) for total residues of narasin. *Federal Register* 05/09/01
Pfizer, Inc. (NADA 8-622)	Oxytetracycline hydrochloride (Terramycin®)	Swine. For the treatment of various bacterial diseases of livestock.	**ORAL—**The supplement provides for a revised withdrawal time for use of oxytetracycline hydrochloride soluble powder in the drinking water. The supplement provides for a zero-day slaughter withdrawal time. *Federal Register* 05/29/01

□

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
HFV-12
Rockville MD 20857

Official Business
Penalty for Private Use $300

PRESORTED STANDARD
POSTAGE AND FEES PAID
PHS-FDA
PERMIT NO. G-285

Use of funds to print the **FDA Veterinarian** has been approved by the Office of Management and Budget.

01-5600