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Center for Veterinary Medicine
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CVM Advisory Committee Reviews Microbial Safety of Pending Veterinary Antimicrobial

At the October 13 Veterinary Medical Advisory Committee (VMAC) meeting, Pfizer Animal Health presented information about tulathromycin, a new animal drug that the company hopes to market for the treatment of swine and bovine respiratory disease.

The VMAC review is one of the risk management mitigations available under Guidance for Industry #152 (GFI #152), which describes a model qualitative risk assessment that the Center may use in evaluating microbial safety for antimicrobial drugs available for veterinary medicine.

In 1999, CVM officially stated that it would consider the potential risks to human health from the development of bacteria resistant to antimicrobial drugs before approving any antimicrobial for use in food animals. FDA is in the process of reviewing the microbial food safety of all animal drugs and has outlined a recommended process for demonstrating the safety of antimicrobials for use in food-producing animals under GFI #152. Last year, CVM released the final version of GFI #152, in which the Center explained an approach for evaluating whether an antimicrobial new animal drug was safe with respect to public health hazards resulting from the development of antimicrobial resistance.

Speakers at the October 13 Veterinary Medicine Advisory Committee meeting to review the food microbial safety of a new animal drug application for an antimicrobial, the first such meeting under Guidance for Industry #152, are (L-R) Dr. Linda Tollefson, Deputy Director, Center for Veterinary Medicine; Dr. John Powers, lead Medical Officer for Antimicrobial Drug Development and Resistance Initiatives in the Office of Drug Evaluation, Center for Drug Evaluation and Research; Dr. Mike Apley, associate professor in the Department of Veterinary Diagnostic and Production Animal Medicine at Iowa State University; Dr. Scott Brown, Senior Director of Metabolism and Safety in Veterinary Medicine R&D at Pfizer Animal Health, the sponsor of the new animal drug that was subject of the meeting; and Dr. Stephen Sundlof, Director, Center for Veterinary Medicine.

FDA review

For antimicrobial drugs, GFI #152 characterizes the hazard as human illness, caused by antimicrobial resistant bacteria. The resistant bacteria must have come from an animal-derived food, and the source of the food must have been an animal treated with an antimicrobial that is also important in human medicine.

Under GFI #152, the risk assessment is made up of three parts.

- Release assessment, which is an estimate of the probability that the proposed use of the antimicrobial new animal drug in food-producing animals will result in the emergence or selection of resistant bacteria in the animal treated with the antimicrobial.
- Exposure assessment, which describes the likelihood of human

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CVM Advisory Committee Reviews Microbial Safety... (Cont.)

exposure to foodborne bacteria of human health consequence through a particular exposure pathway, in this case animal-derived food products.

- Consequence assessment, which addresses the human health consequence associated with bacteria that are resistant to antimicrobial drugs. Part of the consequence assessment is the importance of the antimicrobial in human medicine.

According to GFI #152, if an initial assessment indicates that sufficient hazard exists, the next step is a further risk assessment evaluation. Tulathromycin was subject to a qualitative risk assessment process as outlined in GFI #152. Tulathromycin is a member of the macrolides class of antimicrobials and is in the consequence assessment category of "critically important" because macrolides are used for the treatment of infections caused by *Campylobacter* spp., which is a foodborne human pathogen and associated with food from animals, and because macrolides are important for treating other human diseases, including the potentially fatal "Legionnaire's Disease."

Based on the risk assessments, products are put into a low, medium or high risk category. Corresponding risk management strategies can be applied. One of the risk management steps can be a VMAC review of the application and risk management plans. Tulathromycin is the first product reviewed by VMAC under GFI #152.

Pfizer Animal Health's description of the safety of the drug

At the VMAC meeting, a representative of Pfizer presented information about the drug and the microbial safety steps the product would require.

Pfizer Animal Health said the product should create no microbial safety concerns because the drug would substantially bind to material in the feces and the remaining unbound drug would be sensitive to the pH in the animal's colon, thus reducing the drug's activity. The company also said that *Campylobacter*, which is the bacterium of concern, is more likely to acquire resistance through chromosomal mutation, not gene acquisition, which means tulathromycin is less likely to cause the development of resistance.

Pfizer Animal Health noted that beef and pork typically have *Campylobacter* contamination rates of 0-5%. And historical data indicate that pork and beef do not pose a significant risk for *Campylobacter* that can cause human disease.

In addition, Pfizer Animal Health noted that other macrolides have been in use for more than 30 years in humans, pets and food-producing animals, but resistance found in *Campylobacter* isolates from humans has remained at 3% or lower. (Other animal-use macrolides are erythromycin, tylosin and tilmicosin.)

According to the company, the proposed use of tulathromycin would limit the potential for the development of resistance because the product would be authorized for use only by or on the order of a veterinarian. In addition, the drug is to be used in a single injection, thus further reducing the exposure of bacteria of human health concern to the drug in the treated animals; therefore, the proposed conditions of use (may) minimize the likelihood of resistance development among those bacteria.

CVM concurred with the assessment presented by Pfizer Animal Health.

Role of VMAC

Under GFI #152, FDA has the option of applying several risk management steps involving antimicrobial drugs for food animals, ranging from denying the approval to approving the application under various use conditions that would assure the safe use of the product.

One of risk management options allows FDA to convene an advisory committee to discuss the application before CVM has completed its review of the application. For the review of tulathromycin, CVM convened its VMAC. In addition, this VMAC meeting also included members of the Center for Drug Evaluation and Research's Anti-Infective Drugs Advisory Committee, who are specialists in human diseases caused by bacteria, including resistant bacteria.

According to its charter, VMAC includes a core of voting members with certain expertise, and FDA can add members as necessary to expand the committee's level of expertise. The VMAC includes experts in veterinary medicine, microbiology, biometrics, toxicology, pharmacology, chemistry, animal science and public health. Also, the committee includes a consumer representative.

VMAC questions

CVM asked the VMAC whether the members believe that the sponsor's assessment demonstrated that the product is safe with respect to the potential for transfer of antimicrobial resistant organisms to humans. FDA did not ask the VMAC to decide whether the drug should be approved, but only whether the microbial food safety risk management steps were sufficient to protect public health. CVM will continue to review Pfizer's application and will ultimately decide on the product's approvability for the indicated purpose.

CVM made a point of reviewing the microbial food safety of the product in an open and public meeting as a way to allow public access to the process that FDA is using to review antimicrobial animal drugs.

FDA VETERINARIAN

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FDA Brings Residue-Avoidance Message to Livestock Producers

by Diana Monaco, Public Affairs Specialist, and Beverly Kent, Assistant to the Director, FDA New York District Office

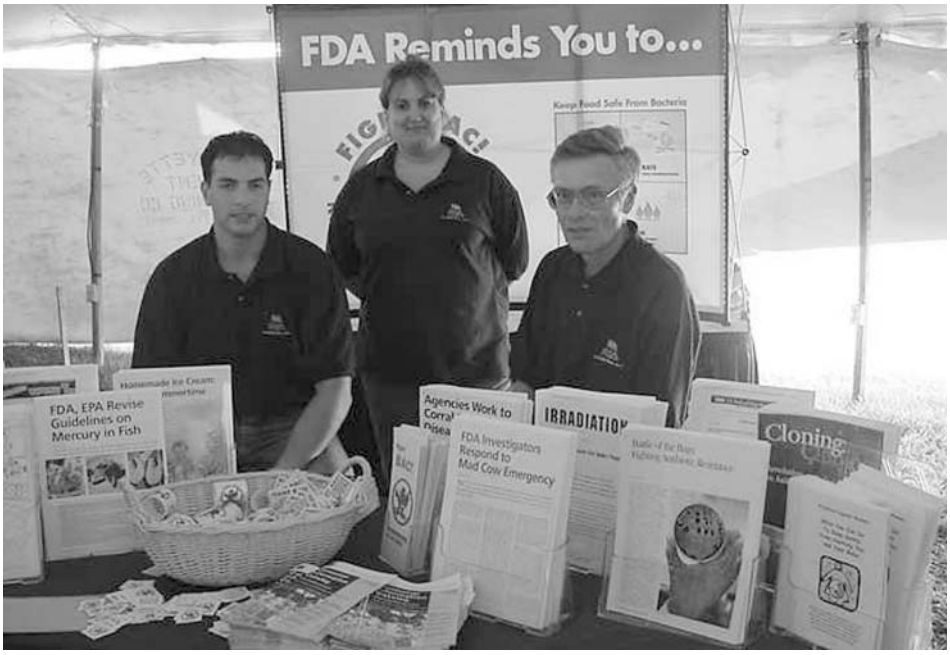
Exhibits at trade shows provide one of the best means of educating livestock producers about the need to avoid illegal drug residues in food-producing animals. So, the Food and Drug Administration's (FDA) New York District Office this year continued its exhibit program started last year at two important farmer meetings.

New York District Office investigators Nick Mendiola, Steve Libel, Bruce Cooper, and Bill Chilton along with public affairs specialist Diana Monaco and assistant to the Director, Beverly Kent, took the FDA exhibit in August to Empire Farm Days in Seneca County in rural New York. The show is one of the largest on the East Coast and attracts about 75,000 visitors from the United States and Canada.

The FDA staff answered questions about veterinary medicine, including ways to avoid illegal drug residues.

The second farm event was the Central New York Farm Progress Show held in Mohawk, NY, in September. This event was targeted at the smaller farm communities and supported by the local elementary schools. Hundreds of children and their parents visited the FDA exhibit and learned about the Agency and its role in agriculture. The event, although smaller in scale compared with the Empire Farm Days, provided an opportunity to educate future farmers.

Ms. Monaco and Ms. Kent coordinated FDA's exhibit program for these events.



Putting a face on FDA: Investigator Nick Mendiola, Public Affairs Specialist Diana Monaco, and Investigator Steve Libel from FDA's New York District Office staff a booth at New York State's Empire Farm Days. The Farm Days program draws approximately 75,000 visitors from the United States and Canada, and provides FDA officials with one of the best opportunities possible to bring the message about the need for livestock producers to avoid illegal drug residues in the food-animals they produce.

CVM Approves First 4-Way Combination Drug

The Center for Veterinary Medicine (CVM) recently approved the first four-way drug combination product under the Animal Drug Availability Act of 1996 (ADAA) that eased the requirements for combination approvals.

Before ADAA, a drug sponsor had to prove the effectiveness of each drug in the combination drug. Under ADAA, the sponsor faces no additional requirements to prove effectiveness of combinations made up of previously approved drugs. The sponsor needs only to show that each drug brings an additional claim to the combination and the drug's safety is not diminished.

ADAA, which CVM supported, changed several rules concerning animal drugs. It created the system of feed mill licensing, so that feed mills would no longer need separate approved applications for each medicated feed. ADAA also allowed CVM to create the category of Veterinary Feed Directive drugs. This category allows certain drugs to be used in feed under the supervision or on the order of a veterinarian.

ADAA also required FDA to publish a final rule defining "adequate and well-controlled" for field studies. It amended the definition of "substantial evidence" of effectiveness in permitting more flexibility in studies to prove a drug's effectiveness. It asked FDA to develop a report on changes that would help get drugs for minor species or minor uses approved, and changed the law so that sponsors were entitled to presubmission conferences.

For combination drugs, ADAA "streamlined the process" and removed

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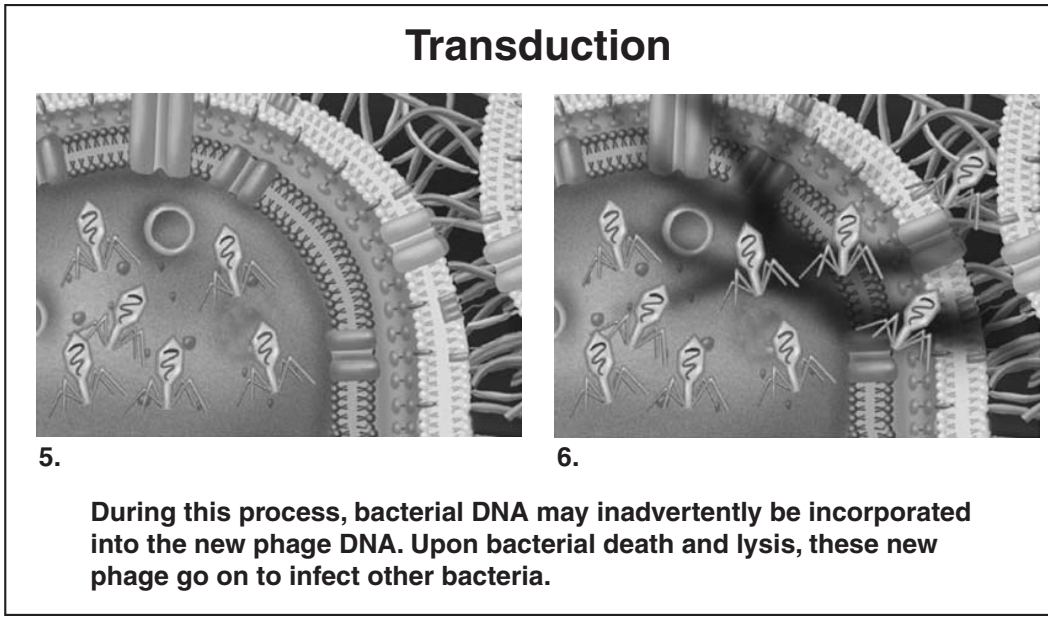
CVM Produces Animation Showing How Bacteria Become Resistant

To make the concept of antimicrobial resistance more understandable to all potential audiences, the Center for Veterinary Medicine (CVM) has created a 9-minute animated video that depicts the ways bacteria typically acquire resistance to antimicrobial drugs.

The Food and Drug Administration (FDA) has taken several steps to address the issue of antimicrobial resistance, which is a concern to physicians as well as food safety specialists. CVM is addressing the public health threat from the development of resistance in foodborne bacteria resulting from the use of antimicrobials in food-producing animals. CVM considers antimicrobial resistance to be one of its top priorities.



One of the images created for an animation developed by the Center for Veterinary Medicine depicting the process of bacteria acquiring resistance to antimicrobial drugs.

The purpose of the video is to advance understanding by key audiences, particularly veterinary students and livestock producers, of the issue of antimicrobial resistance by showing how the process works.

Dr. Robert Walker, director of CVM's Division of Animal and Food Microbiology, and Dr. David White, a research microbiologist in the division, served as subject matter experts on the animation. They developed and explained the molecular and microbiological concepts. FDA's Center for Devices and Radiological Health provided the production personnel.

Vash Klein, the project officer who oversaw the development of the animation, said, "We believe that an obstacle to understanding the issue of antimicrobial resistance is that it seems too abstract. The animated video was developed to help make the concept of antimicrobial resistance more real and understandable. We hope this animation will make the concept more accessible to non-scientists and that it will generate interest in and support for the Center's activities to address the issue of antimicrobial resistance."

The color video animation demonstrates how bacteria can develop resistance to antimicrobial drugs. It further explores the mechanisms of resistance as well as the genetics of resistance transfer. Along with the animation, the video includes text and a "voice over" that explains what is occurring in the video.

The animation is available at: *http://www.fda.gov/cvm/antimicrobial/antimicrobial.html* and may be downloaded and used by anyone who wishes to do so.

. . . 4-Way Combination Drug *(Cont.)*

certain regulatory hurdles, according to Dr. Dan Benz, an animal scientist with the Ruminant Drugs Team at CVM. He pointed out that one of the drugs in the four-way combination, Optaflexx, was approved just a little over a year before the four-way combination product was approved.

The recently approved four-way combination product is an over-the-counter Type A medicated feed article approved for use in heifers fed in confinement for slaughter. The product is made up of four previously approved products—Optaflexx (ractopamine hydrochloride), Rumensin (monensin sodium), Tylan (tylosin phosphate) and MGA (melengestrol acetate). The sponsor is Elanco Animal Health.

The four-way combination product is approved for increased rate of weight gain, improved feed efficiency increased carcass leanness, the prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes* and suppression of estrus.

How CVM Uses Adverse Drug Experience Reports System

The Center for Veterinary Medicine (CVM) collects and analyzes Adverse Drug Experience (ADE) reports to detect problems that may appear after a product has been in use. The ADE report system is complex and goes far beyond simply tallying numbers of complaints. Here's a glimpse at the program's workings, provided by the head of the program at CVM, ***Victoria Hampshire, VMD, Adverse Events Coordinator****.*

CVM cited ADE reports in the recent decision to recall a veterinary product. Does CVM determine actions based strictly on the number of ADEs it receives concerning a product, or are there other considerations?

No. CVM does not make decisions about products based solely on the number of ADE reports it receives. CVM makes a careful analysis of all relevant factors that might affect reporting patterns, such as what is happening in the group of animals taking similar drugs in the class and what animal handlers, owners and veterinarians are doing. Usually, we can come up with a label change that will reduce or eliminate an adverse experience. However, if label changes or packaging changes do not reduce or eliminate the adverse events, then CVM can take other regulatory actions, such as request a recall of the product.

CVM utilizes experienced clinical veterinarians as safety reviewers. The reviewers highlight adverse events that are unusually frequent or severe, as determined based on patterns of events and knowledge in the cohorts (which are same drug or similar drugs in same species, same route). CVM decides what actions by the drug sponsor would be appropriate to eliminate problems that become apparent through the ADE system.

What conditions or trends do you have to see before you take action against a product?

It depends upon the product. What is acceptable for a drug used to treat an old age condition, such as a non-steroidal anti-inflammatory drug for arthritis, would not be tolerable for a preventive used in a wellness program. Also, before we would take action, we would need to see increasing severity and frequency of an adverse event that was unexpected (not on the label), or one that we could not explain.

What actions other than a recall have been triggered by ADEs?

We have required label changes, changes in the dispensing apparatus, and box warning and prescriber information. We've required label changes for clomipramine for liver signs, carprofen and deracoxib for liver signs, enrofloxacin for rare events of blindness, etogesic for dry eye (KCS), moxidectin paste for slippage of the locking mechanism and accidental overdoses in horses, and increased box warnings, and prescriber information for tilimicosin to reduce and we hope eliminate human safety issues.

Are ADEs that prompt a label change fundamentally different than those that prompt a recall?

Yes. The actions prompting a label change mean that FDA feels that the label change will result in a significant reduction of the problem or condition, or will result in a change in prescribing advice that will lead to more judicious selection of candidates. The issues leading to a recall or withdrawal are related to conditions where the cause of the safety problem cannot be easily determined, thus the product cannot be labeled in such a way that adverse events can be reduced to a level of frequency or severity that is expected in the same population taking the same class of drugs for the same reasons.

What is the significance of the fact that the ADE program is partially voluntary? Does that mean the ADE reports are more significant? And what part of the program is voluntary, because aren't the drug firms required to send ADEs to CVM?

Drug sponsors are required to report adverse event reports they receive regardless of whether the source is a veterinarian or the owner of the animal. The voluntary process relates to the fact that the veterinarian is not required to report an ADE to the firm.

The reports represent an index of suspicion that the drug caused the problem. The firm must report it at that point. FDA can then determine how likely it was that the drug was associated with the problem, based on what is known from the pre-approval studies and the label, and similar experience encountered in the post-approval period.

Because reporting is voluntary on behalf of the veterinarian, it is classically associated with under-reporting. Veterinarians don't always associate the reaction with the drug and, if they do, they may become busy and forget to call the firm.

What are the qualifications of the ADE reviewers?

ADE reviewers at CVM must have at least five years of clinical practice, preferably also bolstered by advanced training in academia, regulatory or research background, current licensure and continuing education. Our reviewers have, combined, more than 70 years of veterinary clinical experience, spanning large animal, emergency and critical care; biomedical research support; microbiology; public health; and large animal reproduction.

(Continued, next page)

Ask CVM

The CVM Home Page receives quite a bit of mail. The questions and answers featured here are composites of multiple questions the Home Page has received on the same topic. If you would like to send a question to the CVM Home Page, please visit ***www.fda.gov/cvm*** *and select "contact CVM," or write us directly at* ***CVMHomeP@cvm.fda.gov***

I have a developed a dog food or treat and want to manufacture and market it. Are there rules or requirements I should know about?

Yes, you should be aware of Federal and State rules governing the manufacture and sale of pet food products. Some of the information you should know is on CVM's Website at *www.fda.gov/cvm*. This information applies whether you want to produce pet treats, gravies or other pet food items, and the information applies whether you are manufacturing the products in your house or in a commercial operation. The information applies to all pet food products sold in the United States. Here's an overview of information available about the Federal and State rules.

The FDA's regulation of pet food is similar to that for other animal feeds. There is no requirement that pet food products have premarket approval by the FDA. However, the Federal Food, Drug, and Cosmetic Act (FFDCA) requires that pet foods, like human foods, be pure and wholesome, safe to eat, produced under sanitary conditions,

(Continued, next page)

How CVM Uses Adverse Drug Experience Reports System *(Continued)*

Is the ADE system for animal drugs similar to that for human drugs? What are the similarities? What are the differences?

The systems are very similar in the sense that we use many of the same methods for evaluating safety and efficacy. Common principles in evaluating drug causal relationships include previous experience with the drug or class of drugs, alternative etiologic causes, timing of the reactions, and what happens when the drug is withdrawn or re-introduced. They are different in that the veterinary medicine target animals vary much more in physiology at the level of family, genus and species, than does the human population.

We heard statements recently about "unfiltered reports" about drug experiences being sent to CVM. What's an "unfiltered report?"

An unfiltered report is an ADE report that the drug sponsor receives from a veterinarian or animal owner because the veterinarian or owner suspects that a drug was related to a clinical sign in the animal patient. Drug sponsors are required to report adverse event reports they receive. It means every report gets sent to the Food and Drug Administration and CVM whether the drug was used according to the label instructions or not. The firm may express an opinion about the reaction and CVM may agree or disagree with the opinion after reviewing the report using the ADE evaluation process.

Does the ADE program conduct other sorts of surveillance activity to see if the FDA Form 1932 reports (the standard report form used to file an ADE) are consistent with what is observed elsewhere?

Yes. First, nobody really knows the incidence of drug reactions, because the number of events is classically under-reported and the number of doses administered is not known. The number of doses administered is not the same as the number of doses the firm sells to practitioners.

The surveillance program personnel also monitor key veterinary Internet chat sites and CVM's ADE phone hotline calls. The personnel also attend professional meetings to survey discussions about the products. We also routinely survey important medical literature and regularly read trade journals.

Most importantly, as practicing clinical veterinarians, most of the safety reviewers routinely use most of the products that CVM regulates so that they have a feel for what is normal as well as what is unexpected. This is a fundamental priority of the safety program and CVM. CVM personnel make no recommendation about any drug in an information vacuum. And CVM has a track record of making recommendations that result in a decrease of adverse reactions.

Other than ADEs, do you get other information from companies about various drug products?

Yes, we obtain information about product defects, so that we can try to determine if the ADEs may be product- or manufacturing-related. We also receive information about doses sold so that we have a feel for whether product use is static, decreasing or increasing, compared with the number of ADE reports. We can never determine with certainty how many doses are administered, but we can determine if overall use is up or down or the same by reviewing the number of doses sold.

Ask CVM *(Continued)*

contain no harmful substances, and be truthfully labeled.

The best source of information about State rules is the Association of American Feed Control Officials (AAFCO). To promote uniform labeling requirements across all States and territories of the United States, AAFCO has developed a set of "Model Regulations for Pet Food and Specialty Pet Food" that are contained in AAFCO's *Official Publication*. Since the AAFCO "Model Regulations" were developed consistent with Federal requirements, they are a useful resource for information on the regulation of pet food.

If you are considering starting a pet food, pet treat, or other animal feed business, either in your house or in a commercial establishment, you should consider visiting the Pet Food page on CVM's Website and getting a copy of AAFCO's *Official Publication*. The AAFCO publication is available either through a local library or by purchasing a copy from the AAFCO. Information on how to order the *Official Publication* is available at *www.aafco.org* in the "Please Select" drop-down menu, by writing to AAFCO at P. O. Box 478, Oxford, Ind., 47971, or by faxing your request to 765-385-1032. The *Official Publication* is updated and published annually.

Here is some of the information provided in the AAFCO publication that prospective pet food product manufacturers and sellers will want to know about.

Labels

As stated above, the requirements for labeling pet foods, treats and other pet food items are specified in a section of AAFCO's *Official Publication*, entitled "Model Regulations for Pet Food and Specialty Pet Food." There are 11 "Model Regulations." Some will apply to home-manufactured treats and foods. "Model Regulation PF2," "Label Format and Labeling," gives the general information that must appear on product labels and refers to some of the other "Model Regulations" for more in-depth specifics.

Under the "Model Regulations," pet food products are expected to contain:

- An appropriate product name;
- The species of pet(s) for which the product is intended;
- A quantity statement for the amount of food in the package or container;
- A guaranteed analysis;
- A list of all ingredients in the product;
- A statement of nutritional adequacy, if required;
- Feeding directions, if required; and,
- Name and address of the manufacturer or distributor.

Product name and intended species

According to the AAFCO publication, the name of the product should fairly represent what the product is. An example of a name that unfairly represents a product to be something other than what it is would be "Beef Juice Gravy for Dogs," when the product was composed of water and corn starch. Often the species for which the product is intended is incorporated into the product name, such as the words "for Dogs" in the above example. It is recommend that the name of each species for which the product is intended be presented on the label in words, because pictures or vignettes may be insufficient to clearly indicate the species of intended use.

Quantity statement

The AAFCO publication also has provisions about the quantity statement, which is probably better known as the "net weight" or "net contents" statement.

The quantity statement should appear in the bottom third of the "principal display panel." This panel is the part of the label most likely to be displayed when the product is offered for sale. The quantity statement should be separated from other statements around it. The amount of separation or space above and below the quantity statement must be at least the height of the lettering used in the quantity statement. So, if you use ¼ in. lettering in the quantity statement, you should have a ¼ in. of clear space above and below the quantity statement. You should also have a clear space before and after the quantity statement that is two times the width of the letter N used in the word "Net" in "Net Contents" or "Net Quantity."

Net contents are generally expressed in terms of weight or count for dry products and fluid measures for liquids. Weight should be in terms of avoirdupois (pounds, ounces) units. Metric units of weight (kilograms [kg] grams [g]) may be voluntarily expressed in parentheses after the avoirdupois units. Units of liquid measure should be in terms of U.S. gallon, or quart, pint and fluid ounce and subdivisions thereof. Metric units of volume (liters [L] or milliliters [ml]) may be voluntarily expressed in parentheses after the U. S. liquid measure.

Guaranteed Analysis

According to the AAFCO model regulations, all pet food products should have a section of the label titled "Guaranteed Analysis." For most products, guarantees should be given for the minimum percentage of crude protein, the minimum percentage of crude fat, the maximum percentage of crude fiber and the maximum percentage of moisture.

Guarantees for other nutrients may be needed if the product is promoted as containing significant amounts—or being a good source—of specific nutrients. Other nutrients may also be guaranteed voluntarily as specified in "Model Regulation PF4."

The values for nutrient content are determined by specific gravimetric (weight) and chemical analyses on representative samples of the product.

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Ask CVM *(Continued)*

These analyses can be obtained from various sources. First, there are commercial food and feed analysis laboratories throughout the United States that will do the analysis for a fee. Second, many land grant universities, or their agricultural extension offices, have forage or feed testing laboratories that may be able to perform the analyses for a fee or as a service to residents of the State. Third, some State feed control offices have a feed analysis laboratory associated with the office that may perform the analyses on request. The *Official Publication* lists the contact information for the feed control offices in each State.

A specific number (e.g., 21%), not a range (e.g., 18-25%), and a statement as to whether that number is a minimum or a maximum, must be stated for each guarantee. Values for minimum content indicate the product contains at least the amount listed and will analyze as containing at least that amount of the nutrient within the allowed analytical variation listed for that nutrient in the *Official Publication*. Values for maximum content indicate the product contains no more than the amount listed and will analyze as containing no more than that amount of the nutrient, again within the allowed analytical variation.

The guaranteed values should be representative of the actual nutrient content of the product and cannot be simply picked or set artificially low in the case of minimums, or high in the case of maximums.

Because it is unlikely that the exact same value for each nutrient will be obtained when different batches of the same formulation (recipe) of the product are analyzed, it is helpful to know what the typical variation is for each of the guaranteed nutrients. You can determine the variation by analyzing at least three—and preferably more—batches of the product to determine the variability for each nutrient being guaranteed. The exact number of batches analyzed will be determined by the available resources, the time between batches and the variability observed for the nutrient. If variability is large, more batches are required to assess the extent of the variability and to set guaranteed values with respect to the allowed analytical variances in the *Official Publication*. This is somewhat of an iterative process. If you are unsure of what to set for a particular guarantee based on actual analytical results, you should consider consulting individuals experienced in interpreting analytical results and variability.

Ingredients

Under the AAFCO model regulations, all pet food products should have a section of the label containing a list of the ingredients in the product. All ingredients should be listed by their common or usual name, and in descending order of predominance by their weight in the product. All ingredients should be listed in the same size letters or type. Thus, the ingredient weighing the most in the product is listed first, the ingredient weighing the second most is listed second, and so on, until all ingredients are listed.

Statement of nutritional adequacy

Products that are clearly identified as "treats," "snacks" or "supplements" are not required to have a statement of nutritional adequacy on their label. But nothing prevents you from voluntarily placing a statement of nutritional adequacy on your label.

According to the *Official Publication*, products that may be interpreted by statements on their label to be the sole source of daily nutrients, other than water, required by the animal to which the product is fed should have a statement informing the purchaser how it was determined that the product meets the animal's daily nutrient needs for its stage of life as specified in "Model Regulation PF7," sections (a), (b), or (c) or that the product is intended for intermittent or supplemental feeding only.

Feeding directions

Products with a statement of nutritional adequacy indicating that the product will meet the nutritional requirements for one or more stages of life of the animal to which the product is fed, including treats, snacks, and supplements that make a claim for nutritional adequacy, must have feeding directions that are consistent with meeting the animal's daily nutrient requirements from the product, according to AAFCO. Feeding directions should be in common terms of product usage that are practical for the average user to measure.

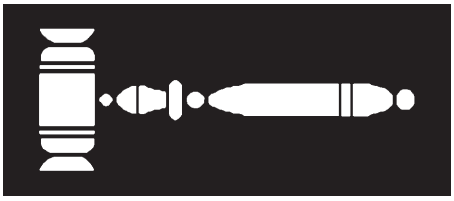
Name and address of manufacturer or distributor

The manufacturer (i.e., if you make the product and sell it) or distributor (i.e., if you have the product made for you and sell it) must list their name and address on the product label, according to the AAFCO publication. The address must include the street address, city, State, and zip code. The street address may be omitted if your firm is listed in the current city directory or telephone directory for the city listed on the label.

Product and manufacturer registration and licensing

Most States require that products distributed in that State be registered or licensed (the term differs between the States) with the State's feed control office. The *Official Publication* lists the name and address for the feed control official and office in each of the 50 States. The *Official Publication* also contains a table of fees charged by each State for registering or licensing products and facilities. If you sell product in a State or ship it direct to individual purchasers in a State as a result of Internet or mail-order sales, then the product should be registered in that State.

Regulatory Activities



The following individuals and firms received Warning Letters for offering animals for slaughter that contained illegal tissue residues of animal drugs:

- John M. Troost and Jeff J. Troost, Partners, J Troost Dairy, Chowchilla, CA
- James W. Jacobs, Owner, Jacobs Ranch L.L.C., Sulphur, OK
- Joe Nottenkamper, Owner, Beebe, AR
- José Gregorio Toledo, Owner, Hatillo, PR
- Alan D. Vander Horst, Owner, Sierra Dairy, Stephenville, TX
- George Houser, Owner, Brotherhood Farms, Greenwich, NY
- Roy Luth, Owner, Roy and Gladice Luth Farm, Harvard, IL
- Albert Haier, Partner, Beck Farms, LP, Freeville, NY
- Sid Leyendekker, Hidden Valley Dairy, Mabton, WA
- Richard M. Nystuen, Owner, Bombay Dairy, Kenyon, MN
- Geoffrey Vanden Heuvel, Owner, J & D Star Dairy, Chino, CA

The above violations involved penicillin in dairy cows, oxytetracycline in a cow, flunixin meglumine in dairy cows and neomycin in bob veal calves.

A Warning Letter was issued to Richard D. Hansen, DVM, CEO, The Veterinary Pharmacy, Inc., Newcastle, OK, after an inspection of the firm's process for compounding and distributing single-dose Biobullet® drug products (containing ivermectin or ceftiofur sodium) for use in food producing animals and horses. The inspection documented significant violations of the Federal Food, Drug and Cosmetic Act (FFDCA) and the Animal Medicinal Drug Use Clarification Act and its implementing regulations at Title 21 of the *Code of Federal Regulations* (CFR) Part 530, Extralabel Drug Use in Animals. The letter said the company's "compounding using the bulk API (active pharmaceutical ingredient) is not permitted under the Animal Medicinal Drug Use Clarification Act."

A Warning Letter was issued to Donald E. Hamilton, President/Owner, Illini Feeds, Inc., Aledo, IL, for significant deviations from the requirements set forth in Title 21 *Code of Federal Regulations* (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). The inspection revealed that salvaged pet food containing prohibited material was added as an ingredient to the swine products manufactured at the facility, and the firm failed to label the non-ruminant products with the required cautionary statement, "Do not feed to cattle or other ruminants."

A Warning Letter was issued to Joel Newman, CEO/President, United Cooperative Farmers, Inc., Fitchburg, MA, for significant deviations from Current Manufacturing Practice (cGMP) regulations for medicated feeds. The deviations include failure to conduct periodic potency assays during the calendar year on at least three representative samples of each feed required to be manufactured by a licensed medicated feed mill, failure to maintain an accurate daily inventory record for each drug used, and failure to accurately indicate the quantity and condition of drugs received on drug receipt records.

A Warning Letter was issued to Edward Richardson, EdD, Interim President, Auburn University, Auburn, AL, after an FDA inspection was conducted to evaluate the performance of the University as a sponsor of Investigational New Animal Drugs (INADs). The inspection focused on one INAD. Based on the evaluation of the information provided in the documents reviewed in the course of the inspection, FDA concluded the drug sponsored by the University is unsafe under section 512 of the FFDCA and adulterated under section 501(a)(5) because the University did not operate in accordance with the implementing regulations for section 512(j) of FFDCA. The violations included a failure to provide current monitoring and documents with missing and unexplained data. In addition, the University was not aware that it is listed as the sponsor for INADs issued by the Center for Veterinary Medicine. 21 CFR Part 511 contains the requirements for the use of a new animal drug for investigational use under an exemption. The sponsor of the INAD is responsible for adhering to the regulations.

A Warning Letter was sent to Robert A. Collins, President, Impro Products, Inc., Waukon, IA, for marketing several "Whey Blend" products not covered by an approved New Animal Drug Application. The labeling and packaging for these products indicate that they are intended for use, among other things, in the cure, prevention, and treatment of disease in animals and/or to affect the structure or function of their bodies, causing the products to be drugs as defined by the FFDCA.

Clarification

The May/June 2004 issue of *FDA Veterinarian* contained a description of a Warning Letter issued to a Shawnee, KS, company because the company failed to label food for cats with the cautionary statement, "Do not feed to cattle or other ruminants." To clarify, FDA does not require such cautionary labels on food for pet cats. However, it does require the cautionary statement on food for exotic zoo cats. The firm cited in the Warning Letter manufactured food for exotic zoo cats, and therefore was required to label the food with the cautionary statement.

CVM Releases NARMS Retail Meat Survey Results

The Center for Veterinary Medicine (CVM) on September 30 released its first annual National Antimicrobial Resistance Monitoring System (NARMS) retail meat survey report, which provides data on the prevalence of antimicrobial resistant foodborne pathogens and commensal bacterial among retail meat and poultry samples.

The data for the report were generated in a 2002 survey. To gather the data, personnel from laboratories in six participating States collected approximately 40 retail meat samples from retail sites each month during the year. The retail meat samples they collected from each site consisted of 10 samples each of chicken breasts, ground turkey, ground beef and pork chops.

The NARMS retail meat surveillance represents a collaborative effort of the Food and Drug Administration, the Centers for Disease Control and Prevention (CDC), and the Foodborne Diseases Active Surveillance Network (FoodNet).

NARMS retail meat surveillance was initiated in 2002 after a feasibility study was conducted in Iowa. Participating 2002 FoodNet laboratories include those from Connecticut, Georgia, Maryland, Minnesota, Oregon and Tennessee. By January 2004, the number of FoodNet laboratories had increased to 10, with the addition of New York, California, Colorado and New Mexico.

The NARMS retail meat surveillance represents a collaborative effort of the Food and Drug Administration, the Centers for Disease Control and Prevention (CDC), and the Foodborne Diseases Active Surveillance Network (FoodNet).

For the NARMS survey, retail meat samples are collected from local grocery stores by participating FoodNet laboratory personnel. A similar retail meat sampling scheme is followed by all NARMS FoodNet participants. All FoodNet laboratories culture for *Campylobacter* and *Salmonella* using standard methods described by FDA. Four sites (Georgia, Maryland, Oregon and Tennessee) also culture for the presence of enterococci and *E. coli* using FDA-described methods.

FoodNet laboratory personnel ship the bacterial isolates to CVM's Office of Research in Laurel, MD. Upon receipt of the isolates, the Office of Research confirmed the identity of the bacteria and developed a comprehensive antibiogram (which is the antimicrobial susceptibility profile of an organism) for the *Salmonella, E. coli* and enterococcal isolates using the NARMS antimicrobial panels. Agar dilution is used to determine antimicrobial susceptibility patterns of *Campylobacter* species.

Antimicrobial susceptibility results are interpreted, where appropriate, according to internationally recognized standards established by the National Committee for Clinical Laboratory Standards (NCCLS). NCCLS is an international, voluntary standards-developing organization for healthcare.

All *Salmonella* and *Campylobacter* isolates are also subjected to Pulsed-field gel electrophoresis (PFGE) to determine genetic relatedness. Resultant PFGE patterns are submitted to the CDC-led PulseNet program, which is a national network for DNA fingerprinting of foodborne pathogens.

Results

Results from the survey demonstrate that retail meats, in particular chicken breast, are contaminated with *Campylobacter*, including antimicrobial resistant variants. *Salmonella* may also be found on retail meats, in particular ground turkey. However, further studies are needed to determine the relationships between antimicrobial use in animal husbandry and the development of antimicrobial resistance in these organisms. In addition, more study is needed to explore mitigation strategies to reduce the presence of these foodborne pathogens on retail foods of animal origin.

The researchers said their observations also suggest that *Enterococcus* spp. and *E. coli* commonly contaminate retail meat products and that differences observed in antimicrobial susceptibility phenotypes may reflect the extent of use of antimicrobials in specific food animal production environments.

Enterococci of foodborne origin have not been conclusively identified as direct causes of clinical infections. Also, with the possible exception of *E. coli* O157:H7 and other shiga-toxin producing strains, the current data are insufficient to accurately assess the

(Continued, next page)

CVM Releases NARMS Retail Meat Survey Results *(Continued)*

hazard and the potential public health risk associated with the presence of generic *E. coli* in foods, regardless of their antimicrobial resistance traits. Further study is also warranted to determine the significance and virulence potential of these organisms that contaminate retail food of animal origin.

All of the data are available in a full report on CVM's website at *http://www.fda.gov/cvm/index/narms/2002retailmeat/coversheet.htm*.

Campylobacter

In 2002, 2,513 retail meats were analyzed for the presence of *Campylobacter* and *Salmonella*. This included 616 chicken breasts, 613 pork chops, 642 ground beef and 642 ground turkey samples. *Campylobacter* was isolated more frequently from chicken breast (47%) than from the other three meat types tested (ground turkey, 0.6%; pork chop, 0.8%; ground beef, 0.0%). *C. jejuni* was the predominant *Campylobacter* species identified, followed by *C. coli*.

In 2002, 2,513 retail meats were analyzed for the presence of* Campylobacter *and* Salmonella*. This included 616 chicken breasts, 613 pork chops, 642 ground beef and 642 ground turkey samples.

Because there are presently no NCCLS-approved interpretive criteria (susceptible, intermediate, or resistant breakpoints) for *Campylobacter*, "resistance" refers to those isolates exhibiting ciprofloxacin minimum inhibitory concentrations (MICs) of > 4 µg/ml and erythromycin MICs of > 8 µg/ml. Fifteen percent of *C. jejuni* recovered from chicken breast exhibited minimum inhibitory concentrations (MIC) > 4 µg/ml to ciprofloxacin, as compared with 10% of *C. coli*. Nineteen percent of *C. coli* recovered from chicken breast exhibited MICs > 8 µg/ml to erythromycin, as compared with no *C. jejuni* (0%).

Salmonella

Salmonella was recovered from ground turkey (12%) more often than the other three meat types tested (chicken breast, 10.0%; pork chop, 1.6%; ground beef, 1.4%). *S.* Heidelburg was the predominant serotype recovered (n=35/153) and was more often associated with ground turkey samples (60%).

Overall, antimicrobial resistant phenotypes differed by *Salmonella* serotype and retail food of animal origin. For example, five multi-drug resistant *S.* Newport were recovered from ground beef, ground turkey and pork chops. The majority of *S.* Newport isolates exhibited resistance to at least nine antimicrobials, including cephalosporins, phenicols, and potentiated sulfonamides. Thirteen percent of *Salmonella* isolates exhibited resistance to gentamicin, and 11% of *Salmonella* isolates demonstrated resistance to ceftiofur. Nalidixic acid resistant *Salmonella* were isolated only from ground turkey and were predominantly *S.* Saintpaul (n=4/6). All isolates were susceptible to ciprofloxacin and ceftriaxone; however, a decrease in susceptibility to ceftriaxone was noted among ceftiofur resistant isolates. Indistinguishable *Salmonella* genetic DNA fingerprints (PFGE patterns) were also recovered from different retail meats collected at different sampling times, and from different States. This information suggests a possible common origin of particular *Salmonella* serotypes.

Enterococcus and E. coli

With regards to *Enterococcus* and *E. coli* prevalence, 1,574 meats were analyzed (only four of the NARMS/FoodNet sites participate in *E. coli/Enterococcus* surveillance). This included 390 chicken breasts, 390 pork chops, 399 ground beef and 395 ground turkey samples.

Sixty-eight percent of these retail meat samples were contaminated with *E. coli*. The majority of the 1,070 *E. coli* isolates recovered were susceptible to the antimicrobials tested. However, 52% were resistant to tetracycline, 36% to streptomycin, 27% to sulfamethoxazole, 19% to ampicillin and 14% to gentamicin.

Ninety-seven percent of the 1,574 retail meat samples were contaminated with enterococci. Among the 1,520 enterococci speciated, *Enterococcus faecalis* was the predominant species recovered (59%), followed by *E. faecium* (33%) and *E. hirae* (7%). Resistance to linezolid or vancomycin was not detected in any isolate, but high-level gentamicin resistance was observed in 9% of enterococci isolates and 52% (excluding *E. faecalis* isolates, which are intrinsically resistant) demonstrated resistance to quinupristin-dalfopristin.

Buying Unapproved Veterinary Drugs From Abroad Can Expose Pets to Unnecessary Risks

Buying an unapproved veterinary drug from outside the United States may expose a pet to an unnecessary health risk.

Drugs that are imported from other countries have not gone through Food and Drug Administration (FDA) review and are therefore considered unapproved new animal drugs under the Federal Food, Drug and Cosmetic Act. To be considered an approved new animal drug, FDA requires a manufacturer or sponsor to prove that the drug is safe and effective. Foreign drugs may not have gone through the study processes needed to meet the safety and efficacy requirements. Moreover, FDA has no way of guaranteeing that these unapproved drugs were properly formulated, stored, shipped and handled—even information about the unapproved drug's country of origin is often questionable.

These concerns apply both to unapproved prescription and over-the-counter drugs. Neither can be legally imported.

FDA has the authority, in conjunction with the U.S. Customs Service, to detain unapproved animal drugs that are being imported into the country. Significant civil and criminal penalty action can be taken against parties seeking to import illegal drugs for commercial distribution.

Approvals for July and August 2004

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

SIMPLICEF Tablets (Cefpodoxime proxetil) filed by Pharmacia and Upjohn Co., a division of Pfizer, Inc. (NADA 141-232). The product is for veterinary prescription use in dogs for treatment of skin infections (wounds and abscesses) caused by susceptible strains of *Staphylococcus intermedius, S. aureus, Streptococcus canis* (group G, -hemolytic), *Escherichia coli, Pasteurella multocida,* and *Proteus mirabilis*. Notice of approval was published August 30, 2004.

MECADOX and TERRAMYCIN (Carbadox and Oxytetracycline) Type A medicated articles to formulate two-way combination drug Type C medicated feeds for swine, filed by Phibro Animal Health (NADA 141-211). The Type C medicated feeds are for use in swine for treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* susceptible to oxytetracycline, for treatment of bacterial pneumonia caused by *Pasteurella multocida* susceptible to oxytetracycline; and for increased rate of weight gain and improved feed efficiency. Notice of approval was published August 18, 2004.

OPTAFLEXX, MGA, and RUMENSIN (Ractopamine hydrochloride, Melengestrol acetate, and Monensin sodium) for Type A medicated articles, filed by Elanco Animal Health (NADA 141-234). The NADA provides for the Type A medicated articles to make three-way combination Type C medicated feeds to be used for increased rate of weight gain, improved feed efficiency, and increased carcass leanness; for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*; and for suppression of estrus (heat) in heifers fed in confinement for slaughter during the last 28 to 42 days on feed. Notice of approval was published August 18, 2004.

(Continued, next page)

Approvals for July and August 2004 *(Continued)*

New Animal Drug Applications (Continued)

- OPTAFLEXX, MGA, RUMENSIN, and TYLAN (Ractopamine hydrochloride, Melengestrol acetate, Monensin sodium, and Tylosin phosphate) filed by Elanco Animal Health for Type A medicated articles (NADA 141-233). The NADA provides for the Type A medicated articles to make four-way combination Type C medicated feeds used for increased rate of weight gain, improved feed efficiency, and increased carcass leanness; for prevention of coccidiosis due to *E. bovis* and *E. zuernii;* for suppression of estrus (heat); and for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium) pyogenes* in heifers fed in confinement for slaughter during the last 28 to 42 days on feed. Notice of approval was published August 18, 2004.

- PREVICOX (Firocoxib) filed by Merial Ltd. (NADA 141-230). The NADA provides for the veterinary prescription use of Firocoxib chewable tablets in dogs for the control of pain and inflammation associated with osteoarthritis. Notice of approval was published August 18, 2004.

- SEDIVET1% Injection (Romifidine hydrochloride) filed by Boehringer Ingelheim Vetmedica, Inc. (NADA 141-229). The NADA provides for the veterinary prescription use of romifidine hydrochloride injectable solution in adult horses as a sedative and analgesic to facilitate handling, clinical examinations, clinical procedures, and minor surgical procedures, and as a pre-anesthetic to the induction of general anesthesia in adult horses. Notice of approval was published August 5, 2004.

- EXCEDE for Swine Sterile Suspension (Ceftiofur crystalline free acid) filed by Pharmacia & Upjohn Co., a division of Pfizer, Inc., (NADA 141-235). The NADA provides for the veterinary prescription use of ceftiofur crystalline free acid suspension in swine, by intramuscular injection, for the treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae, Pasteurella multocida, Haemophilus parasuis,* and *Streptococcus suis.* Notice of approval was published July 23, 2004.

- SURPASS Topical Cream (1% Diclofenac sodium) filed by IDEXX Pharmaceuticals, Inc. (NADA 141-186). The product is for topical use in horses for the control of pain and inflammation associated with osteoarthritis in tarsal, carpal, metacarpophalangeal, metatarsophalangeal and proximal interphalangeal (hock, knee, fetlock, and pastern) joints. Notice of approval was published July 7, 2004.

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

- ZIMECTERIN GOLD PASTE (Ivermectin [1.55%] and Praziquantel [7.75%] oral paste) filed by Merial Ltd. (NADA 141-214). The supplemental NADA provides for revised labeling for the use in horses for the treatment and control of various internal parasites. Specifically, the supplement amends product labeling to separate parasite life stages in the indications section, to remove the 8-week re-treatment interval from the dosage and administration section, and to add a new precaution statement. Notice of approval was published August 12, 2004.

(Continued, next page)

Approvals for July and August 2004 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

- DECTOMAX Pour-On Solution for Cattle (Doramectin) filed by Pfizer, Inc. (NADA 141-095). The supplemental applications provides for an increased period of protection from reinfection with three species of internal parasites following topical administration of doramectin solution on cattle. Specifically, the period of persistent effectiveness is increased from 21 days to 28 days for *Cooperia oncophora*, from 28 days to 35 days for *Cooperia punctata*, and from 21 to 28 days for *Dictyocaulus viviparous*. Notice of approval was published August 10, 2004.

- NAXCEL Sterile Powder for Injection (Ceftiofur sodium) (NADA 140-338) and EXCENEL RTU Ceftiofur hydrochloride (NADA 140-890) filed by Pharmacia and Upjohn, a division of Pfizer, Inc. The supplemental NADAs provide for establishing a 4-day pre-slaughter withdrawal period in swine injected with either product. The products are indicated for the treatment and control of swine bacterial respiratory disease (swine bacterial pneumonia) associated with *Actinobacillus (Haemophilus) pleuropneumoniae, Pasteurella multocida, Salmonella choleraesuis,* and *Streptococcus suis* type 2. Notice of approval was published August 5, 2004.

- DECCOX and RUMENSIN (Decoquinate and Monensin sodium) Type A medicated articles, filed by Alpharma Inc. (NADA 141-148). The supplemental NADA provides for the use of single-ingredient Decoquinate and Monensin Type A medicated articles to make two-way Type B and Type C medicated feeds for cattle at a broader range of concentrations of 12.9 to 90.8 grams per ton of feed. The product is indicated for the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, and improved feed efficiency in cattle being fed in confinement for slaughter. Notice of approval was published August 30, 2004.

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

- Prescription use of Oxytocin Injectable Solution, filed by Cross Vetpharm Group, Ltd. (ANADA 200-328). The product is for use in ewes, sows, cows and horses. It is indicated to be used as a uterine contractor to precipitate and accelerate normal parturition and postpartum evacuation of uterine debris. In surgery, it may be used postoperatively following cesarean section to facilitate involution and resistance to the large inflow of blood. It will contract smooth muscle cells of the mammary gland for milk letdown if the udder is in proper physiological state. Cross Vetpharm Group's Oxytocin Injection is approved as a generic copy of Phoenix Scientific Inc.'s PVL Oxytocin Injectable approved under NADA 124-241. Notice of approval was published July 9, 2004.

- SPECMED Scour-Chek (Spectinomycin dihydrochloride pentahydrate) filed by Cross Vetpharm Group. Ltd. (ANADA 200-364). The product is for the oral use in pigs under 4 weeks of age for the treatment and control of infectious bacterial enteritis (white scours) associated with *Escherichia coli*. Cross Vetpharm Group's SPECMED Scour-Chek is approved as a generic copy of Phoenix Scientific, Inc.'s SPECTAM Scour Halt, approved under NADA 033-157. Notice of approval was published August 30, 2004.

(Continued, next page)

Approvals for July and August 2004 *(Continued)*

Abbreviated New Animal Drug Applications (Continued)

PENNCHLOR and BMD (Chlortetracycline Type A and Bacitracin methylene disalicylate medicated articles), filed by Pennfield Oil Co. (ANADA 200-358). The ANADA provides for the use of single-ingredient Type A medicated articles to make two-way combination drug Type B and Type C medicated feeds for swine for increased rate of weight gain and improved feed efficiency; for treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline hydrochloride. Pennfield Oil Co.'s product is approved as a generic copy of Alpharma, Inc.'s BMD and ChlorMax NADA, approved under 141-059. Notice of approval was published August 18, 2004.

VETRO-GEN Veterinary Ophthalmic Ointment (Gentamicin sulfate), filed by Altana, Inc. (ANADA 200-273). The product is for use on dogs and cats for topical treatment of conjunctivitis caused by susceptible bacteria. Altana's product is approved as a generic copy of Schering-Plough Animal Health's GENTOCIN Ophthalmic Ointment approved under NADA 98-989. Notice of approval was published August 5, 2004.

Ivermectin Chewable Tablets, filed by Phoenix Scientific, Inc., (ANADA 200-297). The ANADA provides for the veterinary prescription use of chewable ivermectin tablets in dogs to prevent canine heartworm disease by eliminating the tissue stage of heartworm larvae (*Dirofilaria immitis*) for 1 month (30 days) after infection. Phoenix Scientific, Inc.'s Ivermectin Chewable Tablets for Dogs are approved as a generic copy of Merial Ltd.'s HEARTGARD Chewables, approved under NADA 140-886. Notice of approval was published July 22, 2004.

HAN-PEN (Penicillin G Potassium) Soluble Powder, filed by G. C. Hanford Manufacturing Co. (ANADA 200-372). The product is for use in the drinking water of turkeys for the treatment of erysipelas caused by *Erysipelothrix rhusiopathiae*. G. C. Hanford Manufacturing Co.'s product is approved as a generic copy of Fort Dodge Animal Health's Penicillin G Potassium, USP, approved under NADA 55-060. Notice of approval was published July 9, 2004.

ESTROPLAN (Cloprostenol sodium) Injection filed by Parnell Laboratories (Aust) Pty. Ltd. (ANADA 200-310). The product is for the use by veterinary prescription for manipulation of the estrous cycle of cattle. Parnell Laboratories (Aust) Pty. Ltd.'s ESTROPLAN Injection is approved as a generic copy of Schering-Plough Animal Health Corp.'s ESTRUMATE, approved under NADA 113-645. Notice of approval was published on July 7, 2004.

(Continued, next page)

Approvals for July and August 2004 *(Continued)*

CVM has published in the *Federal Register* notice of the approval of this Supplemental Abbreviated New Animal Drug Approvals (ANADA)

AGRIMYCIN 166 (Oxytetracycline hydrochloride) Soluble Powder filed by Agri Laboratories, Ltd. (ANADA 200-066). The product is for use in chickens, turkeys and swine to make medicated drinking water for the treatment of various bacterial diseases of livestock. The supplemental NADA provides for a new package size (9.87 oz. [280 g]) and change of strength of oxytetracycline. The product is approved in chickens for control of infectious synovitis caused by *Mycoplasma synoviae*; for control of respiratory disease (CRD) and air sac infections caused by *Mycoplasma gallisepticum,* and *Escherichia coli;* and for control of fowl cholera caused by *Pasteurella multocida*; in turkeys for control of Hexamitiasis caused by *Hexamita meleagridis*; control of infectious synovitis caused by *Mycoplasma synoviae*, and in growing turkeys for control of complicating bacterial organisms associated with bluecomb (transmittal enteritis, coronaviral enteritis); and in swine for the control and treatment of the following diseases: bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis*; bacterial pneumonia caused by *Pasteurella multocida*; and in breeding swine for leptospirosis (reducing the incidence of abortions and shedding of leptospira) caused by *Leptospira pomona.* Notice of approval was published August 11, 2004.

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