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Center for Veterinary Medicine
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Judicious Use of Antimicrobials for Aquatic Veterinarians

by Donald A. Prater, DVM, Leader, Aquaculture Drugs Team, Center for Veterinary Medicine

A new booklet describing principles of judicious use of antimicrobials for aquatic veterinarians was scheduled for release at the Aquaculture America meeting in Las Vegas, NV, in February 2006.

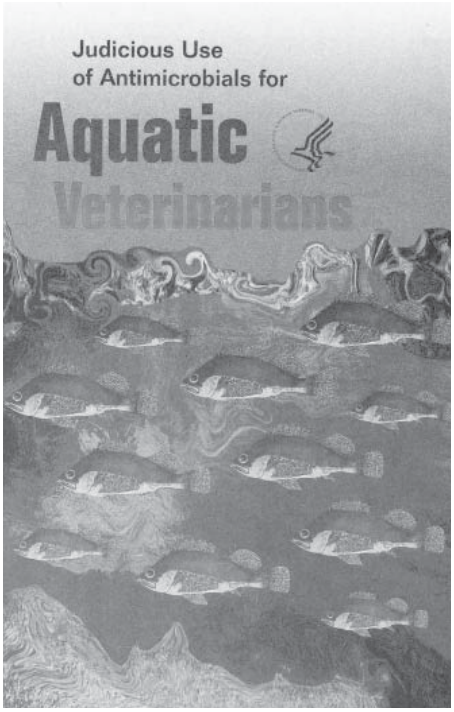
The booklet, *Judicious Use of Antimicrobials for Aquatic Veterinarians*, is a collaborative effort between the Aquatic Veterinary Medicine Committee of the American Veterinary Medical Association (AVMA) and the Aquaculture Working Group of the Food and Drug Administration's Center for Veterinary Medicine (CVM).

The work is intended as a reference and educational resource for practitioners administering antimicrobials primarily to food fish, although the application of judicious and prudent use of antimicrobial drugs applies to the treatment of other types of aquatic animals, as well.

The booklet is the first guide produced for a minor species.

Currently, three antimicrobials are approved to treat various bacterial diseases in fish – oxytetracycline, sulfadimethoxine/ormetoprim, and florfenicol. All are administered as medicated feed. Oxytetracycline (Terramycin® 100 for Fish) and sulfadimethoxine/ormetoprim (Romet® 30) are approved for over-the-counter use.

In salmonids, Terramycin® 100 for Fish is approved to control ulcer disease caused by *Haemophilus piscium*, furunculosis caused by *Aeromonas salmonicida*, bacterial hemorrhagic septicemia caused by *Aeromonas liquefaciens*, and pseudomonas disease. This use has a 21-day withdrawal time. In catfish, it is approved to control bacterial hemorrhagic septicemia caused by *Aeromonas liquefaciens* and pseudomonas disease. This use has a 21-day withdrawal time. In lobsters, it is used to control gaffkemia caused by *Aerococcus viridans,* and this use has a 30-day withdrawal time.



Romet® 30 is approved to control furunculosis in salmonids (trout and salmon) caused by *Aeromonas salmonicida*. This use has a 42-day withdrawal time. In catfish, Romet® 30 is approved for the control of enteric septicemia of catfish caused by *Edwardsiella ictaluri*. It has a 3-day withdrawal time. The treatment regimen for both indications is 50 mg per kilogram of body weight for five consecutive days.

Under the Food and Drug Administration's Compliance Policy Guide 615.115, "Extralabel Use of Medicated Feeds for Minor Species," veterinarians may use oxytetracycline and sulfadimethoxine/ormetoprim to treat additional diseases or additional species, provided the medicated feed is produced in accordance with approved label directions. (The Compliance Policy Guide is available at *http://www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg615-115.html*.)

In October 2005, florfenicol (Aquaflor®) was approved as a Veterinary Feed Directive (VFD) drug for the control of mortality in catfish due to enteric septicemia of catfish associated with *Edwardsiella ictaluri*. The treatment

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regimen for this indication is 10 consecutive days of therapy at a dose of 10 mg per kilogram of body weight. The withdrawal time is 12 days prior to harvest.

VFD drugs are available only upon the order of a licensed veterinarian. (Extralabel use of VFD drugs is strictly prohibited.)

VFD categorization of Aquaflor® is consistent with CVM's policy for approving new antimicrobials for use in medicated feeds. VFD status limits access to the antimicrobial and places it in the hands of prescribers with training and experience in the diagnosis and treatment of disease in populations of animals.

The veterinary profession shares the concerns of the public, governmental agencies, and the public health community regarding the broad issue of antimicrobial resistance and specifically the risk of resistance developing in animals with subsequent transfer to humans.

Judicious Use

The booklet describes concerns for the development of antimicrobial resistance and outlines principles for the use of antimicrobials in veterinary practice. The veterinary profession shares the concerns of the public, governmental agencies, and the public health community regarding the broad issue of antimicrobial resistance and specifically the risk of resistance developing in animals with subsequent transfer to humans.

In 1998, the AVMA started a profession-wide initiative, including companion and food animal practitioner groups, to develop and implement judicious use principles for the therapeutic use of antimicrobials by veterinarians. A general set of principles was approved emphasizing the need for veterinarians to strive to optimize therapeutic efficacy and minimize resistance to antimicrobials to protect public and animal health.

The 15 principles described in the new booklet are followed by a section discussing their application to large populations of fish, such as those treated in food fish aquaculture. Although veterinarians have not traditionally been the primary providers of health care to cultured fish species, the growing number and scale of cultured fish operations, in addition to backyard ponds and home aquaria, in the United States has resulted in the expanding involvement of veterinary practitioners.

The approval of the new antimicrobial, as a VFD drug, and the opportunity to utilize medicated feeds for minor species in an extralabel fashion has resulted in an important increase in the therapeutic options for aquatic veterinarians. This increase in therapeutic options is accompanied by an increased responsibility for judicious use of antimicrobials. The new booklet will be a substantial resource for these practitioners.

For a copy of the booklet, contact Dr. David Scarfe, Assistant Director, Scientific Activities Division at the American Veterinary Medical Association, 1931 N. Meacham Rd., Suite 100, Schaumburg, IL 60173; Direct phone – (847) 285-6634; (800) 248-2862 Ext 6634; *Dscarfe@AVMA.org*. Or contact the Communications Staff, FDA/Center for Veterinary Medicine, 7519 Standish Place, HFV-12, Rockville, MD 20855; 240-276-9300.

Federal Government Developing Response to Avian Influenza Concerns

The outbreak of avian influenza (AI) in Asia and reaching west and south is caused by a virus that could mutate and could cause a human influenza epidemic or even pandemic, which is why the Federal Government is heavily engaged in developing a response to this threat.

The virus responsible for the outbreak of AI that started in Asia has shown that

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Editor's Note

The *FDA Veterinarian* production schedule has been delayed, which is why this issue is dated September-October 2005. However, we will publish all of the issues, including the final issue from 2005, as soon as possible.

FDA VETERINARIAN

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...Response to Avian Influenza Concerns *(Continued)*

it can cause serious illness in humans, even death, but as of mid-February health officials had reported fewer than 200 cases of human infections. The risk to humans is clear, though, especially if the virus becomes highly contagious in humans.

Health officials have identified the strain of AI first reported in Asia as H5N1, and they considered it to be highly pathogenic, or "high-path" (HPAI), in poultry, which means that it usually kills poultry infected by it. It also efficiently transfers between sick and healthy birds, so it is highly contagious among poultry.

But the AI first seen in Asia has not caused many reported human illnesses. The humans who have become ill from the influenza are those who had close contact with infected poultry or, in rare cases, with other individuals, usually relatives, who were infected. So, although the disease can jump the "species barrier" between poultry and people, which concerns scientists and public health officials, at this point it does not appear to do so efficiently, and it does not appear to spread between people efficiently, either. Consequently, the disease is widespread in poultry flocks, but not in the human population.

The HPAI first reported in Asia is caused by a Type A virus. All viruses that can infect poultry are Type A. The category of Type A viruses also includes viruses that infect mammals, including humans, as well as birds. If the HPAI seen in Asia somehow picks up a genetic trait that makes it more contagious among humans – either by mutating or by acquiring genes from another virus – and it is highly pathogenic in humans, then we could face a human influenza pandemic.

President Bush has already responded to the pandemic threat by issuing the "National Strategy for Pandemic Influenza," which outlines the roles and responsibilities of the Federal, State, and local governments, industry, international partners, and individuals in preparing for and responding to an influenza pandemic. More information about the White House's response is available at *www.whitehouse.gov/homeland/pandemic-influenza.html*.

Health and Human Services Secretary Michael Leavitt in November said that the Department of Health and Human Services (HHS) has developed the HHS Pandemic Influenza Plan, and he directed all operating units of HHS, which includes the Food and Drug Administration, the parent Agency of the Center for Veterinary Medicine, to develop operational plans.

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More information about the Federal Government's preparations is available at *www.pandemicflu.gov.*

Scientific evaluation

Scientists classify all Type A influenza viruses by subtype based on the characteristics of two proteins on the surface of the virus – hemagglutinin and neuraminidase, which are abbreviated as H and N (as in H5N1).

Most people in the United States have developed immunity to some influenza viruses, but the U.S. population probably does not have much of a natural immunity to H5 viruses.

Bacteria are relatively stable, genetically, compared to viruses. In fact, influenza viruses are significantly more likely than bacteria to incorrectly reproduce themselves. Those mistakes, or mutations, can give the virus new characteristics, possibly including the ability to efficiently infect humans.

Influenza viruses are also capable of acquiring genes from another strain of influenza virus, a process called "re-assortment." In that process, basically two different viruses occupying the same cell in a host animal (which could be a human) exchange genes. Because Type A influenza viruses can be found in humans as well as other mammals and birds, the avian influenza viruses have opportunity to re-assort genes with viruses that can infect humans, potentially giving the AI virus the ability to infect humans, causing severe illness, and spread efficiently between humans.

However, the fact that AI is present in an area does not mean that humans will become infected. The United States has seen outbreaks of HPAI in birds in previous years. In 1924, an outbreak was recorded in East Coast live bird markets. In 1983-84, an HPAI outbreak in the Northeast was contained, but authorities had to destroy about 17 million chickens, turkeys, and guinea fowl. The most recent HPAI outbreak was in 2004, when the disease was seen in the southern United States. U.S. Department of Agriculture, State, and local authorities were able to quickly contain and eliminate the disease.

Therefore, the mere presence of HPAI in birds does not automatically mean a human influenza epidemic or pandemic. But certain strains of AI carry the risk of a human epidemic, which if not contained could spread and become a pandemic.

CVM Aquaculture Specialist Puts 'PhishPharm' Database of Drug Studies in Aquaculture on Internet

Center for Veterinary Medicine (CVM) aquaculture specialist Dr. Renate Reimschuessel has created a database, which she has named "PhishPharm," of studies about drug metabolism in aquaculture species and made the database available to researchers and others via the Internet. It contains 400 studies now, and will be expanded as additional studies and data become available. As explained in this interview, Dr. Reimschuessel invites users to submit reports of published studies to be included in the database.

FDA Veterinarian: What is "PhishPharm?"

Dr. Reimschuessel: It's a database, originally designed to help me organize a massive literature search, that has developed into a tool that I use frequently when designing experiments. It should also prove very helpful as a source of information for the CVM aquaculture drugs review team and other regulatory scientists. I hope it will be useful to scientists working on drug development for aquatic species both in the United States and abroad.

FDA Veterinarian: What prompted you to develop this database?

Dr. Reimschuessel: CVM held a meeting August 30, 2000, titled "Crop Grouping in Aquaculture." At this meeting, research scientists from Upper Mississippi Environmental Sciences Center, Virginia-Maryland Regional College of Veterinary Medicine, the NRSP-7 (National Research Support Project #7) program, and The Ohio State University presented CVM with data about grouping species for drug approvals. Pharmacokinetic data for several drugs in several fish species were presented. It was clear, though, that much more data were needed to understand how, and at what rates, different fish species metabolize drugs. One of the first steps needed was to compile existing data.

FDA Veterinarian: Is there that much information available about fish?

Dr. Reimschuessel: In general it was assumed that "there is not much known" about fish pharmacokinetics. This assumption is both true and false. Compared with mammalian pharmacokinetics data, there is much less information available for fish. Nevertheless, there is still a wealth of information that has been published over the last 30 years. Unfortunately, this information is located in journals that are fairly specialized and not readily available from an average search of databases, such as MEDLINE.

In order to become more knowledgeable in this area, I began to collect as many articles as possible about drug metabolism and residue depletion in fish. After about 2 years of collecting, I had a stack of about 150 articles in my office and would spend quite a bit of time trying to find specific information that I knew was in one of those articles. I decided it was necessary to begin to mine data from these articles, if only by species, by compound tested, and by the citation. I began putting this information into an excel spreadsheet. (Over the summers I would enlist the help of student interns to help mine more of the data from these articles.)

However, I found that besides the information I had started to gather I wanted to know the dose of the compound and how long it was administered. Then I wanted to know at what temperature the fish were held, and if they were in saltwater or freshwater. Later the weight of the animals was added along with more extensive comments on residue levels over time.

Gathering this information took many months and many hours. The spreadsheet grew until it was more than 800 rows long, and again I was faced with something that was getting unmanageable. I could not find the information buried in such a long sheet.

FDA Veterinarian: How did the spreadsheet become the database?

Dr. Reimschuessel: In 2003, I teamed up with Clifford Hodsdon, an independent programmer (contact information is in the PhishPharm database), to convert the data from spreadsheet format into an Access database. With the first iteration it became quite apparent that we needed major revisions in the way we presented the information. All of the data needed to be put into standardized formats for the database program to work. For example, all the weight data that students had put into the database were in the format used in the original articles (pounds, grams, kilograms, etc.) and had to be converted to a standardized format. The same was true for quite a number of fields.

Thus began the long and arduous task of re-working the mined data to get them into formats that the database would be able to sort and provide back in a meaningful form.

Also, over the next two years, with the help of the CVM librarian Debbie Brooks, the list of articles grew to more than 400. The number of fields and amount of details mined from the articles also grew.

It was about this time that the goal of organizing this material for my own use changed to one of developing a publishable database so others would be able to benefit from our efforts.

(Continued, next page)

12th Annual FDA Science Forum Scheduled

Each year since 1993, the FDA Science Forum has served as an important venue for communication between FDA scientists and stakeholders on scientific topics of vital regulatory concern.

This is the exclusive annual event at which scientists from all disciplines and organizational components of FDA meet with their counterparts from industry and academia to share data, knowledge, and ideas on the science-based mission of the Agency.

This year's Science Forum will take place April 18-20 at the Washington, DC, Convention Center. This year's Science Forum features plenary presentations by leaders of the academic and public health communities, numerous general sessions, and a poster session, which will provide an excellent environment for an open discussion of how emerging science and technology can be effectively applied in support of the FDA's national public health mission.

FDA is the first scientific agency in the world to have been transformed into a full-fledged regulatory agency. At the Agency's Centennial and at the Science Forum, it is important to revisit that investment in regulatory science and communicate not only the tangible results of that investment, but highlight the process by which that original commitment to high quality scientific achievement will translate into the future of science at FDA.

The 2006 FDA Science Forum offers a valuable opportunity for industry and academia to learn about FDA's science programs, collaborative opportunities, and regulatory priorities. For more information, please see *www.fda.gov/scienceforum*.

...'PhishPharm' Database... *(Continued)*

This new goal meant that the database entries needed to be proofread multiple times by several different people to ensure accuracy.

FDA Veterinarian: When did you first post the database?

Dr. Reimschuessel: We posted it in October 2005, so it's relatively new.

FDA Veterinarian: How often will it be updated?

Dr. Reimschuessel: We plan to update the information yearly.

FDA Veterinarian: Have you disseminated information about the database?

Dr. Reimschuessel: Our group published an article for American Association of Pharmaceutical Scientists (AAPS) (Reimschuessel R, Stewart L, Squibb E, Hirokawa K, Brady T, Brooks D, Shaikh B, Hodsdon C. Fish Drug Analysis—Phish-Pharm: A Searchable Database of Pharmacokinetics Data in Fish. American Association of Pharmaceutical Scientists Journal 07(02): E288-E327 2005 *http://www.aapsj.org/view.asp?art=aapsj070230*) that used the database to produce a number of graphs that show the half-lives of different drugs in different fish species.

(The database is accessible through this article. Use the link to go to the article, and scroll down through the article to the "zip" links to the database.)

The type of data available through the database for the first time allows us to begin to look at the forest rather than the individual trees. With the information summarized in such a fashion, one can get an overview of the kind of data to expect and how much variability one should expect with a given compound. For example, it was not possible for me to appreciate the metabolic similarity between the many fish species without this kind of data presentation.

FDA Veterinarian: How can someone find out more?

Dr. Reimschuessel: The database is available to be downloaded from the AAPS website. It is an Access database, but it has also been put into a stand alone Application format for users that do not have Access on their computers. I have also made the raw data Excel spreadsheet available for users that would like to be able to view that format.

To access the database, go to http://www.aapsj.org/view.asp?art=aapsj070230 and scroll down to the zip links.

Comings and Goings

New Hires

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Suzanne Wolcoff, Consumer Safety Officer
- Hope Baird, Staff Fellow
- Jennifer Matzscza, Staff Fellow
- Stephine Keeton, Staff Fellow, Mathematical Statistician
- Jocelyn Crawford, Staff Fellow

OFFICE OF MANAGEMENT

- Kathy Eberhart, Training Specialist

Departures

OFFICE OF THE CENTER DIRECTOR

- Ronald Scherzberg, Regulatory Policy Analyst

OFFICE OF NEW ANIMAL DRUG EVALUATION

- C. Ququan, Mathematical Statistician

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Julia Punderson, Consumer Safety Officer
- Margaret Bowman, Staff Fellow

OFFICE OF MANAGEMENT

- Michelle Mathias, Program Analyst
- Eve Princler, Training Specialist

A Look Back at CVM: During 1970s, Division of Nutritional Sciences Added to Scientific Review Sophistication

by Jon F. Scheid, Editor

For the Food and Drug Administration's (FDA) Centennial, FDA Veterinarian *is taking a look back at some of the events that shaped the Center for Veterinary Medicine (CVM). Several significant changes took place in the early 1970s, when the Center developed its expertise in the use of statistics and "experimental design." Here's the story of that change, based on interviews with some of the people who were here at the time.*

In the 1970s, the Bureau for Veterinary Medicine (BVM), which in 1984 became CVM, began employing broader use of statistics and "experimental design," especially for drugs used for livestock production purposes. Before that, BVM relied more on reviewer judgment than probability assessments in deciding whether to approve an animal drug, according to Dr. Woodrow Knight, who was at the Bureau then and was part of the change.

Dr. Knight, who recently retired from his position of Director, Division of Production Drugs, at CVM, said reviewer judgments worked well when reviewing therapeutic drugs. However, he said, "Techniques for reviewing drugs intended to increase the rate of gain, improve marketable milk production, increase egg production, affect carcass quality, or improve feed efficiency in normal, healthy animals were unfamiliar ground" to many on the BVM staff at the time.

Dr. Knight, an animal scientist, was one of the first staff members hired for the Bureau's fledgling Division of Nutritional Sciences. The Division was formally created on February 1, 1971, and staffed with animal scientists, statisticians, and veterinarians.

"The difficulty was how to evaluate drugs that affected small increments of response, normally less than a 10 percent and often less than a five percent response over the negative control treatment," Dr. Knight said. "Contrast this with a therapeutic drug, which often gives a 75 percent response or greater and whose response is very obvious in a disease-response situation."

"It is my understanding" that before the Division of Nutritional Sciences was established "the Center's technical expertise consisted mainly of persons who had years of practical experience in veterinary medicine and who were not trained in the analytical skills of statistics, probability, and experimental design," Dr. Knight said.

Dr. William Price, one of the founders of the Division, and currently a special assistant to the Director of CVM's Division of Animal Feeds, said the changes came about because the BVM Director at the time, Dr. C. D. Van Houweling, had a research background and recognized the need for these additional disciplines in drug review.

After the Division was established, the Bureau hired animal scientists with expertise in statistics and experimental design. Scientists hired at the time included Dr. George Graber, who was hired as an animal nutritionist and is now the Deputy Director of CVM's Office of Surveillance and Compliance, and Dr. Price

Dr. Price was the Chief of the Ruminant Branch in the Division of Nutritional Sciences. He came to the Bureau in the late 1960s with a degree in animal science as well as extensive graduate training in mathematical statistics. Among those Dr. Price hired were Dr. Knight and Dr. Norris Alderson, who now serves as FDA Associate Commissioner for Science, and Director, Office of Science and Health Coordination.

The experimental design and statistical tools that the scientists brought to BVM led to the use of tests and experiments that generated more information. The techniques the Division of Nutritional Sciences brought to the Bureau, for instance, called for designing feeding trials that would use small subgroups, rather than an entire poultry house, for the experimental groups, and then replicate the tests for a more "powerful" result, Dr. Price said.

Also, according to Dr. Graber, "Dose response studies introduced for the first time the ability to allow for effectiveness over a range of drug content in feed, which when coupled with regression analysis permitted interpolation between levels tested."

Growing scientific sophistication

The Division was successful in transferring its techniques throughout the rest of the Bureau. "Our early successes included the incorporation of statistics into the process of evaluating drugs intended for both therapeutic and non-therapeutic uses and for food additive products. We wrote guidelines that became a model for the other units within the Bureau," Dr. Knight said.

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A Look Back at CVM... *(Continued)*

The new ways of scientific review of data allowed BVM to be a significant participant in FDA's effort to remove Diethylstilbesterol (DES) from the market.

According to a history of CVM, prepared in 1989 by Orland Soave, a veterinarian and consultant, DES was approved in 1954 as a growth stimulant for cattle and sheep. However, scientists were able to detect residues of the drug in food from treated animals. In 1974, FDA initially prohibited the use of DES in cattle.

The work BVM did in connection with DES led to a further exploration of the law's requirements about substances labeled as carcinogens. The Division of Nutritional Sciences, with encouragement from then-Chief General Counsel Peter Barton Hutt, developed the early concepts that led to the "Sensitivity of Method" (SOM) regulation.

Certain substances that can technically be labeled carcinogens but can still be safely used in food-producing animals are permitted under Federal law through the "DES proviso." And Federal regulators use the SOM rules to determine when the DES proviso can be applied.

See 21 U.S.C. §360b(d)(1)(I), which presents the DES proviso:

"(I) such drug induces cancer when ingested by man or animal or, after tests which are appropriate for the evaluation of the safety of such drug, induces cancer in man or animal, except that the foregoing provisions of this subparagraph shall not apply with respect to such drug if the Secretary finds that, under the conditions of use specified in proposed labeling and reasonably certain to be followed in practice (i) such drug will not adversely affect the animals for which it is intended, and (ii) no residue of such drug will be found (by methods of examination prescribed or approved by the Secretary by regulations)…in any edible portion of such animals after slaughter or in any food yielded by or derived from the living animals…."

SOM regulations specify procedures for determining the metabolites, the tissues that the metabolites are concentrated in, the safety of the metabolites as determined by animal tests, and the level of the metabolites that would present a minimal cancer risk (specified in the regulation as corresponding "to a maximum lifetime risk to the test animal of one in 1 million") before the drug can be considered for use in animals. Consequently, the regulation used to assess the one in 1 million risk of cancer to animals is written to require that the concentration of the drug in edible tissues be so low as to "cause no significant increase in the risk of cancer to people."

According to Dr. Knight, prior to the development of the SOM regulation, FDA did not have a systematic process for determining the safety of carcinogens added to the food supply.

"Our concern initially related to how to interpret the requirement (in the law prohibiting the use of carcinogens) so that the level of sensitivity for the method that the Secretary would establish to measure the residue resulting from the use of a carcinogen in food-producing animals would not be changing just because scientists developed a more sensitive method. The sensitivity requirements of this method were to be established based on the safe level determined by scientists qualified to make such evaluations. Thus, the SOM document was designed to explain how the Secretary made the determinations of safety for such carcinogens that may be added to the food supply," Dr. Knight said.

The SOM concepts were first developed in 1973 by the members of the Division of Nutritional Science, Dr. Price said. The SOM rule was finalized in 1987 and amended in 2002. The 2002 amendments revised the definition of "no residue" to mean that no residue of the drug is detected with an approved regulatory method under the conditions of use of the drug. The SOM concept is based on metabolism studies and statistical analysis and disciplines, which were the Division of Nutritional Sciences specialty.

Division became part of ONADE

The Division grew to about two-dozen employees by the mid-1970s. Later during the 1970s, Dr. Van Houweling merged the Division of Nutritional Sciences with the Therapeutic Animal Drugs Division to create the Office of New Animal Drug Evaluation (ONADE). The Division of Nutritional Sciences' branches of ruminant, non-ruminant, and poultry drugs were brought into ONADE and expanded to include anthelmintics and hormones. Since then, the departments were put back into their own Division of Production Drugs as the current Ruminant Drug Team and the Swine and Poultry Drug Team. Also, the food additive responsibility was shifted to the Division of Animal Feeds in the Office of Surveillance and Compliance.

According to Dr. Knight, the "big asset of the Division of Nutritional Sciences was that we looked at the data presented by the sponsor and made recommendations based on the detailed analysis of that data using the principles of statistics and experimental design."

Although the Division of Nutritional Sciences no longer exists within CVM, its legacy continues, Dr. Knight, Dr. Price, and Dr. Graber said. The use of statistical analysis and experimental design is now a standard part of the review of most animal drug applications, they said.

BSE INSPECTION UPDATE

CVM Reports BSE Inspection Figures as of November 26

As of November 26, 2005, the Food and Drug Administration (FDA) had received more than 41,000 reports of inspections done under the ruminant feed rule designed to prevent the establishment and spread of bovine spongiform encephalopathy (BSE) in the United States.

Approximately 68 percent of the inspections were conducted by State officials under contract to FDA, with the remainder conducted by FDA officials.

Inspections conducted by State and FDA investigators are classified to reflect the compliance status at the time of the inspection, based upon whether objectionable conditions were documented. Based on the conditions found, inspection results are recorded in one of three classifications:

- **OAI (Official Action Indicated)** when inspectors find significant objectionable conditions or practices and believe that regulatory sanctions are warranted to address the establishment's lack of compliance with the regulation. An example of an OAI classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspectors will promptly reinspect facilities classified OAI after regulatory sanctions have been applied to determine whether the corrective actions are adequate to address the objectionable conditions.
- **VAI (Voluntary Action Indicated)** when inspectors find objectionable conditions or practices that do not meet the threshold of regulatory significance, but warrant an advisory to inform the establishment that inspectors found conditions or practices that should be voluntarily corrected. VAI violations are typically technical violations of the 1997 BSE Feed Rule. These violations include minor recordkeeping lapses or conditions involving non-ruminant feeds.
- **NAI (No Action Indicated)** when inspectors find no objectionable conditions or practices or, if they find objectionable conditions, those conditions are of a minor nature and do not justify further actions.

(Note: The following figures are as of November 26, 2005.)

Renderers

These firms are the first to handle and process (i.e., render) animal proteins. After they process the material, they send it to feed mills and/or protein blenders for use as a feed ingredient.

- **Number of active firms whose initial inspection has been reported to FDA** – 274
- **Number of active firms handling materials prohibited from use in ruminant feed** – 185 (68 percent of those active firms inspected)

  Of those 185 firms:
  - ❖ 1 (0.5 percent) was classified as OAI
  - ❖ 11 (5.9 percent) were classified as VAI

Licensed feed mills

In the inspection report database, FDA lists medicated feed licensed feed mills separately from non-licensed feed mills. But the licensing has nothing to do with handling prohibited materials under the feed ban regulation. FDA requires feed mills to have medicated feed licenses to manufacture and distribute feed using certain potent drug products, usually those requiring some pre-slaughter withdrawal time, to produce certain medicated feed products.

- **Number of active firms whose initial inspection has been reported to FDA** – 1,079
- **Number of active firms handling materials prohibited from use in ruminant feed** – 426 (39 percent of those active firms inspected)

  Of those 426 firms:
  - ❖ 0 were classified as OAI
  - ❖ 8 (1.9 percent) were classified as VAI

Feed mills not licensed by FDA

These feed mills are not licensed by the FDA to produce medicated feeds.

- **Number of active firms whose initial inspection has been reported to FDA** – 5,165
- **Number of active firms handling materials prohibited from use in ruminant feed** – 2,036 (39 percent of those active firms inspected)

  Of those 2,036 firms:
  - ❖ 2 (0.1 percent) were classified as OAI
  - ❖ 24 (1.2 percent) were classified as VAI

Protein blenders

These firms blend rendered animal protein for the purpose of producing feed ingredients used by feed mills.

- **Number of active firms whose initial inspection has been reported to FDA** – 340
- **Number of active firms handling materials prohibited from use in ruminant feed** – 147 (43 percent of those active firms inspected)

  Of those 147 firms:
  - ❖ 0 were classified as OAI
  - ❖ 7 (4.8 percent) were classified as VAI

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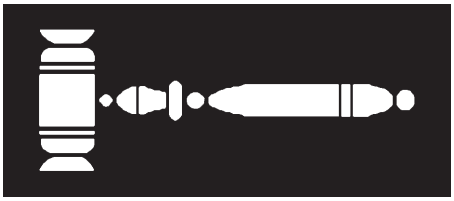
Regulatory Activities



The following individuals and firms received Warning Letters for offering animals for sale for slaughter as food that contained illegal drug residues:

- Abel Villalpando, Sr., owner, Dexter Dairy, Dexter, NM
- Robert Lawson, owner, Lawsons Farm, Irasburg, VT
- Calvin W. Pareo, co-owner, Milk Flow Dairy, Portales, NM

The above violations involved penicillin, flunixin, and sulfadimethoxine in dairy cows.

The presence of the illegal drug residues in edible tissues caused the food to be adulterated.

A Warning Letter was issued to Jerome Fitzgerald, president, Clement Fitzgerald, vice president, and Andrew W. Fitzgerald, secretary-treasurer, Four Brothers Dairy, Inc., Shoshone, ID, because an investigation revealed the presence of illegal drug residues of penicillin in a dairy cow offered for sale for slaughter as food. The penicillin was found to be above the tolerance of 0.05 parts per million established for residues of penicillin in the edible tissues of cattle, which caused the food to be adulterated. The investigation also showed the adulteration of the new animal drug because it was used in a manner that did not conform with its approved labeling. Further there were deviations from the regulations for Extralabel Drug Use in Animals. For example, the penicillin was administered without following the dosage level of treatment or the methods for injecting the drug set forth in the approved labeling and was done so without the supervision of a licensed veterinarian. Also, the drug was administered without following the recommended withdrawal time for the drug set forth in the approved labeling, and was done so without the supervision of a licensed veterinarian. Extralabel use of an approved animal drug that is not in compliance with the regulations renders the drug unsafe under Section 512 and thus adulterated under Section 501(a)(5) of the Federal Food, Drug, and Cosmetic Act (the Act).

A Warning Letter was issued to Walter E. Newton, III, president, WaJa Farms, Inc., New Albany, PA, because an inspection of the veal calf operation confirmed that a veal calf owned by the firm was shipped from a contract grower for sale for slaughter as food that was adulterated because of the presence of neomycin in kidney tissue. Neomycin is not approved for use in veal calves. The inspection also revealed that the firm caused the new animal drugs neomycin and penicillin to become adulterated and unsafe, when in accordance with the firm's

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CVM Reports BSE Inspection Figures... *(Continued)*

Renderers, feed mills, protein blenders

This category includes any firm that is represented by any of the above four categories, but includes only those firms that manufacture, process, or blend animal feed or feed ingredients using prohibited materials.

- **Number of active renderers, feed mills, and protein blenders whose initial inspection has been reported to FDA** – 6,576
- **Number of active renderers, feed mills, and protein blenders processing with prohibited materials** – 539 (8.2 percent of those active firms inspected)

  Of those 539 firms:

  - ❖ 3 (0.6 percent) were classified as OAI
  - ❖ 23 (4.3 percent) were classified as VAI

Other firms inspected

Examples of such firms include ruminant feeders, on-farm mixers, pet food manufacturers, animal feed salvagers, distributors, retailers, and animal feed transporters.

- **Number of active firms whose initial inspection has been reported to FDA** – 13,477
- **Number of active firms handling materials prohibited from use in ruminant feed** – 3,748 (28 percent of those active firms inspected)

  Of those 3,748 firms:

  - ❖ 8 (0.2 percent) were classified as OAI
  - ❖ 95 (2.5 percent) were classified as VAI

Total firms

- **Number of active firms whose initial inspection has been reported to FDA** – 16,476
- **Number of active firms handling materials prohibited from use in ruminant feed** – 4,553 (27 percent of those active firms inspected)

  Of those 4,553 firms:

  - ❖ 9 (0.2 percent) were classified as OAI
  - ❖ 107 (2.4 percent) were classified as VAI

(NOTE: A single firm that has more than one function can be listed in different industry segments, which also means that the total may be less than a combination of all the segments.)

Regulatory Activities *(Continued)*

instructions a contract grower failed to use the drugs in conformance with their approved labeling. Extralabel use, i.e., the actual or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling, is permitted only if the use is by or on the lawful order of a licensed veterinarian within the context of a valid veterinarian/client/patient relationship. The investigation found the extralabel use of Neomycin 325 Soluble Powder in starter formula fed to veal calves, and the extralabel use of Pen-Aqueous Sterile Penicillin G Procaine Injectable Suspension in the treatment of veal calves did not comply with the Extralabel Use in Animals regulations.

A Warning Letter was issued to Michael Mumbulo, Edmeston, NY, because an investigation into his veal calf operation confirmed that he offered an animal for sale for slaughter as food that contained illegal drug residues of neomycin. Neomycin is not approved for use in veal calves. The extralabel use of neomycin without complying with the Extralabel Drug Use in Animals regulations causes the drug to be unsafe and adulterated. The presence of this unsafe drug in edible tissue from the animal causes the food to be adulterated. The investigation also found animals were held under conditions so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply.

Warning Letters were issued to several dairy operations and a cattle operation because investigations confirmed the operations were offering animals for sale for slaughter as food that contained illegal drug residues. The presence of the illegal drug residues in edible tissues caused the food to be adulterated. The investigations also revealed the adulteration of new animal drugs because they were used in a manner that did not conform with their approved labeling. Further, there were serious deviations from the regulations for Extralabel Drug Use in Animals. These deviations caused animal drugs to be used in a manner that was unsafe and adulterated under the Act. In addition, the investigation also found animals were held under conditions so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. The Warning Letters were issued to the following:

- Chuck H. Hilt, owner, C & M Hilt Dairy, Gooding, ID
- Gregory S. Vierstra, owner, Vierstra & Son, Inc. dba Classic Dairy, Twin Falls, ID
- Fritz Balsiger, partner/manager, Balsiger, Greiner, Rohweder Dairy, LLP, Lake Park, MN
- Edgar M. Martin, owner, Edgar Martin Dairy, Brooten, MN
- Richard Leyendekker, farm manager, SLI Dairy, Sunnyside, WA
- Sidney C. De Boer, owner, De Boer Dairy, Burlington, WA
- Tom B. De Groot, partner, De Groot Dairy, LLC, Lynden, WA
- Laverne Morrell, owner, Morrell Farm, Franklin, NY
- Merle R. Buss, dba Rancho, Inc., Shawnee, OK

The above violations involved penicillin, tilmicosin, neomycin, oxytetracycline, sulfadimethoxine, and flunixin in cows.

A Warning Letter was issued to David J. Wright, DVM, partner, Buffalo Equine and Large Animal Clinic, LLP, Buffalo, MN, because an investigation involving the use of drugs in the veterinary practice revealed that an animal drug was caused to be unsafe and adulterated because it was used in a manner that did not conform with its approved uses or the regulations for Extralabel Drug Use in Animals. A brand of sulfadimethoxine injection - 40% was administered to treat peritonitis and mastitis in lactating dairy cattle, which is not an approved use of this drug. The extralabel use of an approved animal or human drug in animals is permitted only if it complies with the regulations set forth in 21 CFR 530. The regulations prohibit the extralabel use of sulfadimethoxine in lactating dairy cattle, except for approved uses. The use by Dr. Wright was not one of the approved uses of sulfadimethoxine injection.

A Warning Letter was sent to Allen M. Petro, owner, Ana-Tech, Monroe, WI, which manufactures and distributes multiple products for both human and animal consumption. The Warning Letter was sent for marketing and distributing several products not covered by an approved New Animal Drug Application (NADA). Section 201(g)(1)(B) of the Act defines a drug as any article intended for the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals. Section 201(v) of the Act defines a new animal drug as one in which the composition is such that the drug is not generally recognized, among experts qualified by scientific training and experience to evaluate the safety and effectiveness of animal drugs, as safe and effective for use under the conditions prescribed, recommended, or suggested in its labeling. New animal drugs may not be marketed in the absence of an approved NADA demonstrating the safety and effectiveness of the product. The representations on the labeling for the firm's products, i.e., X-IT(W) and NO MORE, indicate that they are intended for use in the prevention and treatment of disease in animals. The firm also offers several direct-fed microbial products, which they refer to as "probiotics," which are identified on the firm's internet site as "naturally occurring beneficial organisms that inhibit disease causing organisms." The representations on the website for these direct-fed microbial products establish their intended use in the treatment and prevention of disease in animals. Because none of these products is covered by an approved NADA, the products are unsafe, and thus are adulterated. The Warning

(Continued, next page)

Regulatory Activities *(Continued)*

Letter also includes violations of the Act and FDA regulations concerning several of the firm's products for human consumption.

A Warning Letter was sent to Paul Rasmussen, president, Gold Eagle Cooperative Board of Directors, Corwith, IA, because inspections of the animal feed manufacturing operations in Goldfield, IA, revealed 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 investigation found a failure to label one of the company's products, "ISLACT – IS LACTATION," a swine feed, with the statement "Do Not Feed to Cattle or Other Ruminants," as required by Part 589.2000. Although the swine feed is not formulated with protein derived from mammalian tissues, which is prohibited in ruminant feed, the facility's production practices may cause the finished product to contain such material. The investigator found that the firm does not have a strategy for sequencing feeds and does not flush or otherwise clean shared production equipment between the manufacture of poultry feed formulated with protein derived from mammalian tissues and swine feed formulated without such material. As a result, swine feed may acquire protein derived from mammalian tissue from poultry feed residue remaining on the shared production equipment. The failure to label the swine feed with the above-mentioned statement causes it to be misbranded under the Act.

A Warning Letter was issued to G. Allen Andreas, chairman and chief executive, Archer Daniels Midland Company (ADM), Decatur, IL, for significant deviations from Current Good Manufacturing Practice (cGMP) regulations for medicated feeds at its medicated feed mill in Higginsville, MO. The deviations include a failure to perform assays on representative samples of medicated feeds requiring a medicated feed mill license, the drug inventory records do not accurately reflect the current inventory, the storage of drugs in the mixing area without properly identifying, storing, handling, and controlling the drugs to maintain their integrity and identity.

A Warning Letter was issued to Lawrence S. Hoblik, chief executive officer, J.R. Simplot Company, Boise, ID, for significant deviations from cGMP regulations for medicated feeds at its licensed medicated feed mill Western Stockmen's, Caldwell, ID. FDA's cGMP regulations state that for feeds requiring an approved license for their manufacture and marketing (such as medicated feed containing amprolium) at least three representative samples of medicated feed containing each drug or drug combination used in the establishment shall be collected and assayed by approved methods, at periodic intervals during the calendar year. The FDA investigator observed Western Stockmen's manufactured medicated feed containing amprolium, a Category II, Type A medicated article, without performing any assays. In addition, the Corid 25% Amprolium found at the feed mill was labeled only for the manufacture of medicated feed for calves, however, the firm is also using it to manufacture a Type B medicated feed, called Amprolium Premix, which is labeled for use in chickens, turkeys, and pheasants, in addition to calves. If the firm wants to continue to manufacture medicated feed for these other species, it should use a drug product that is labeled for use in these other species.

A Warning Letter was issued to Larry D. Smith, president, Custom Feed Services Corporation, Norfolk, NE, for significant deviations from cGMP regulations for medicated feeds at its medicated feed mill. The deviations found include master records files and product records are deficient, there is no record the mineral oil scale is calibrated once a year, the facility is not maintained in a reasonably clean and orderly manner, and a proper receipt record for each lot of drug received is not maintained. In addition, the investigation revealed feeds manufactured and distributed by the firm that contain carbon black. Carbon black is a color additive. According to the Act, color additives are deemed to be unsafe unless they are used in accordance with a color additive regulation that specifies the conditions under which the color additive may be safely used, including the purposes for which it may be used and the product category or categories to which it may be added. There is no color additive regulation currently allowing for the use of carbon black in food, including animal feeds. Animal feeds containing carbon black are thus unsafe and adulterated. Also, the labels for feeds containing monensin intended for use in dairy cattle are not in conformance with the approved application. Approval provides for feed to contain 11- 22 g of monensin per ton, but the firm's labels instead state the amount as mg/head/day.

A Warning Letter was issued to Ron Curtis, owner, Cache Commodities, Inc., Ogden UT, because an inspection of the medicated feed mill revealed that the facility manufactured Type C medicated feeds from a Category II, Type A medicated article on several occasions without a FDA medicated feed mill license. According to the Act and FDA regulations, this feed cannot be manufactured without a FDA medicated feed mill license. Because these feeds were manufactured at a facility without a medicated feed mill license, these feeds are considered unsafe and therefore adulterated. Facilities manufacturing solely medicated feeds for which an approved medicated feed mill license is not required must comply with cGMP requirements. FDA investigation revealed that the facility no longer manufactures any medicated

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Regulatory Activities *(Continued)*

feeds that require a medicated feed mill license. Therefore, the facility is subject to the cGMP requirements. An inspection noted the following deviations: failure to establish and use adequate procedures for all equipment used in the production of medicated feeds to avoid unsafe contamination of medicated and non-medicated feeds; failure to establish adequate procedures to aid in assuring the identity, strength, quality, and purity of the Type A medicated articles; the buildings and grounds are not constructed and maintained in such a manner to minimize vermin and pest infestations; and failure to maintain, on the premises, records identifying the formulation, date of mixing, and date of shipment of medicated feeds for one year following the date of last distribution.

Approvals for October, November and December 2005, and January 2006

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

CYDECTIN (moxidectin) Oral Drench for Sheep (NADA 141-247), filed by Fort Dodge Animal Health, Division of Wyeth. The NADA provides for the oral use of moxidectin solution for the treatment and control of the adult and larval (L_4) stages of the following internal parasites of sheep: *Haemonchus contortus, Teladorsagia circumcincta, Teladorsagia trifurcate, Trichostrongylus axei, Trichostrongylus colubriformis, Trichostrongylus vitrinus, Cooperia curticei, Cooperia oncophora, Oesophagostomum columbianum, Oesophagostomum venulosum, Nematodirus battus, Nematodirus filicolis,* and *Nematodirus spathiger*. Notice of approval was published December 23, 2005.

AQUAFLOR (florfenicol) Type A medicated article (NADA 141-246), filed by Schering-Plough Animal Health Corporation. The NADA provides for the use of florfenicol Type A medicated article by veterinary feed directive to formulate Type C medicated feeds for the control of mortality due to enteric septicemia of catfish associated with *Edwardsiella ictaluri*. Notice of approval was published November 21, 2005.

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

RUMENSIN 80 (monensin sodium) Type A medicated article (NADA 95-735), filed by Elanco Animal Health. The supplement provides for the use of RUMENSIN 80 Type A medicated article in Type C medicated feeds fed in component feeding systems (including top dress) used for increased milk production efficiency (production of marketable solids-corrected milk per unit of feed intake) in dairy cows. Notice of approval was published January 11, 2006.

LEGEND Multi-dose (hyaluronate sodium) Injectable Solution (NADA 140-883), filed by Bayer HealthCare LLC, Animal Health Division. The supplemental NADA provides for veterinary prescription use of this hyaluronate sodium solution, formulated with a benzyl alcohol preservative, from a multi-dose vial for intravenous administration to horses for the treatment of carpal or fetlock osteoarthritis. Notice of approval was published January 11, 2006.

(Continued, next page)

Approvals for October 2005 – January 2006 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

RUMENSIN 80 (monensin sodium) Type A medicated article (NADA 95-735), filed by Elanco Animal Health. The supplemental NADA revises the description of growing cattle fed monensin Type C medicated feeds for increased rate of weight gain and for prevention and control of coccidiosis. Notice of approval was published January 3, 2006.

MICOTIL 300 (tilmicosin phosphate)Injectable Solution (NADA 140-929), filed by Elanco Animal Health approved for the veterinary prescription use of an injectable solution of tilmicosin phosphate for respiratory disease in cattle and sheep. The supplemental NADA adds user safety information to product labeling related to the mechanism of toxicity and medical intervention. Notice of approval was published December 20, 2005.

QUEST (moxidectin 2.0%) Gel (NADA 141-087) and QUEST Plus (moxidectin 2.0%/praziquantel 12.5%) Gel (NADA 141-216), filed by Fort Dodge Animal Health, Division of Wyeth. Both products are used for the treatment and control of various species of internal parasites in horses and ponies. The supplemental NADAs provide for use of the products for the treatment and control of two additional species of adult small strongyles, which have been added to the product labeling: adult *Cylicocyclus radiatus* and *Petrovinema poculatus*. The products were already approved for treatment and control of the following parasites in horses and ponies: **Large strongyles** – *Strongylus vulgaris* (adult and L_4/L_5 arterial stages), *Strongylus edentatus* – (adult and tissue stages), *Triodontophorus brevicauda* (adults), *Triodontophorus serratus* (adults); **Small strongyles** (adults) – *Cyathostomum catinatum, Cyathostomum pateratum, Cylicostephanus* spp., including *Cylicostephanus calicatus, Cylicostephanus goldi, Cylicostephanus longibursatus, Cylicostephanus minutus, Cylicocyclus* spp., including *Cylicocyclus insigne, Cylicocyclus leptostomum, Cylicocyclus nassatus, Coronocyclus* spp., including *Coronocyclus coronatus, Coronocyclus labiatus, Coronocyclus labratus, Gyalocephalus capitatus*; **Small strongyles** – undifferentiated luminal larvae; **Encysted cyathostomes** – Late L_3 and L_4 mucosal cyathostome larvae; **Ascarids** – *Parascaris equorum* (adults and L_4 larval states; **Pinworms** – *Oxyuris equi* (adults and L_4 larval stages); **Hairworms** – *Trichostrongylus axei* (adults); **Large-mouth stomach worms** – *Habronema muscae* (adults); **Horse stomach bots** – *Gasterophilus intestinalis* (2^{nd} and 3^{rd} instars), *Gasterophilus nasalis* (3^{rd} instars); Tapeworms – *Anoplocephala perfoliata* (adults). Notice of approval was published December 19, 2005.

ZIMECTERIN GOLD (ivermectin 1.55%/praziquantel 7.75%) Paste (NADA 141-214), filed by Merial, Ltd., is an over-the-counter product for oral use for the treatment and control of the following parasites in horses: **Tapeworms** – *Anoplocephala perfoliata*; **Large strongyles** (adults) – *Strongylus vulgaris* (also early forms in blood vessels), *S. edentatus* (also tissue stages), *S. equinus, Triodontophorus* spp. including *T. brevicauda* and *T. serratus* and *Craterostomum acuticaudatum*; **Small strongyles** (adults, including those resistant to some benzimidazole class compounds) – *Coronocyclus* spp. including *C. coronatus, C. labiatus*, and *C. labratus, Cyathostomum* spp. including *C. catinatum* and *C. pateratum, Cylicocyclus* spp. including *C. insigne, C. leptostomum, C. nassatus*, and *C. breviacapsulatus, Cylicodontophorus* spp., *Cylicostephanus* spp. including *C. calicatus, C. goldi, C. longibursatus*, and *C. minutus*, and *Petrovinema poculatum*; **Small strongyles** – fourth-stage larvae; **Pinworms** (adults and fourth-stage larvae) – *Oxyuris equi*; **Ascarids** (adults and third- and fourth-stage larvae – *Parascaris equorum*; **Hairworms** (adults) – *Trichostrongylus axei*; **Large-mouth stomach worms** (adults) – *Habronema*

(Continued, next page)

Approvals for October 2005 – January 2006 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

muscae; **Bots** (oral and gastric stages) – *Gasterophilus* ssp. including *G. intestinalis* and *G. nasalis*; **Lungworms** (adults and fourth-stage larvae) – *Dictyocalulus arnfieldi*; **Intestinal Threadworms** (adults) – *Strongyloides westeri*; **Summer Sores** caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae; and **Dermatitis** caused by neck threadworm microfilariae of *Onchocerca* sp. The supplemental NADA reduces the minimum age for administration from 5 months to 2 months of age. Notice of approval was published November 21, 2005.

TYLAN (tylosin tartrate) Soluble Powder (NADA 13-076), filed by Elanco Animal Health, for use in honey bees for the control of American foulbrood (*Paenibacillus larvae*). The approval of this supplemental NADA relied on publicly available safety and effectiveness data contained in Public Master File (PMF) 5783, which were compiled under National Research Support Project #7, a national agricultural research program for obtaining clearances for use of new drugs in minor animal species and for special uses. Notice of approval was published November 16, 2005.

EQUIMAX (ivermectin 1.87%/praziquantel 14.03%) Paste (NADA 141-215), filed by Virbac AH, Inc. The supplemental NADA provides revised labeling for ivermectin and praziquantel oral paste used in horses for the treatment and control of various internal parasites. The amended product labeling separates parasite life stages in the indications section. The product is indicated for treatment and control of the following parasites: **Tapeworms** – *Anoplocephala perfoliata*; **Large strongyles** (adults) – *Strongylus vulgaris* (also early forms in blood vessels), *Strongylus edentatus* (also tissue stages), *Strongylus equinus, Triodontophorus* spp.; **Small strongyles** (adults, including those resistant to some benzimidazole class compounds) – *Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp.; **Small strongyles** (fourth-stage larvae); **Pinworms** (adults and fourth-stage larvae) – *Oxyuris equi*; **Ascarids** (adults and third- and fourth-stage larvae) – *Parascaris equorum*; **Hairworms** (adults) – *Trichostrongylus axei*; **Large-mouth Stomach Worms** (adults) – *Habronema muscae;* **Bots** (oral and gastric stages) – *Gasterophilus* spp.; **Lungworms** (adults and fourth-stage larvae) – *Dictyocaulus arnfieldi*; **Intestinal Threadworms** (adults) – *Strongyloides westeri*; **Summer Sores** caused by *Habronema* and *Draschia* spp. cutaneous third-stage larvae; **Dermatitis** caused by **Neck threadworm** microfilariae – *Onchocerca* sp. Notice of approval was published November 1, 2005.

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

EQUIZONE 100 (phenylbutazone) Powder (ANADA 200-334), filed by A & G Pharmaceuticals, Inc. The ANADA provides for the veterinary prescription use of a phenylbutazone powder administered to horses in feed for the relief of inflammatory conditions associated with the musculoskeletal system. A & G Pharmaceuticals, Inc.'s, EQUIZONE 100 is approved as a generic copy of Phoenix Scientific, Inc.'s, Phenylbute (phenylbutazone) Tablets, USP, approved under NADA 91-818. Notice of approval was published January 6, 2006.

(Continued, next page)

Approvals for October 2005 – January 2006 *(Continued)*

Abbreviated New Animal Drug Applications (Continued)

Furosemide (furosemide) Syrup 1% (ANADA 200-373), filed by First Priority, Inc. The ANADA provides for the oral use of furosemide syrup in dogs for the treatment of edema. First Priority, Inc.'s, FUROSEMIDE Syrup 1% is approved as a generic copy of Intervet, Inc.'s, LASIX (furosemide) Syrup 1%, approved under NADA 102-380. Notice of approval was published December 27, 2005.

PRICONAZOLE (miconazole nitrate) Lotion 1% and PRICONAZOLE (miconazole nitrate) Spray 1% (ANADA 200-362), filed by First Priority, Inc. The ANADA provides for topical use of miconazole nitrate on dogs and cats for the treatment of fungal infections caused by *Microsporum canis, Microsporum gypseum*, and *Trichophyton mentagrophytes*. First Priority's PRICONAZOLE Lotion 1% and PRICONAZOLE Spray 1% are approved as generic copies of Schering-Plough Animal Health Corp.'s CONOFITE Lotion 1% and Spray 1%, approved under NADA 95-184. Notice of approval was published December 9, 2005.

SULFAMED-G (sulfadimethoxine) Soluble Powder (ANADA 200-376), filed by Cross Vetpharm Group Ltd. The ANADA provides for the oral use of sulfadimethoxine soluble powder to create a solution administered as a drench to cattle or in the drinking water of chickens, turkeys, or cattle for the treatment of coccidiosis or various bacterial diseases. For broiler and replacement chickens, the product is indicated for the treatment of disease outbreaks of coccidiosis, fowl cholera, and infectious coryza. For meat-producing turkeys, the product is indicated for the treatment of disease outbreaks of coccidiosis and fowl cholera. For dairy calves, dairy heifers, and beef cattle, the product is indicated for the treatment of shipping fever complex, bacterial pneumonia, calf diphtheria, and foot rot. Cross Vetpharm Group Ltd.'s SULFAMED-G Soluble Powder is approved as a generic copy of Pfizer, Inc.'s ALBON (sulfadimethoxine) Soluble Powder, approved under NADA 46-285. Notice of approval was published December 9, 2005.

TETRAMED 324 HCA (tetracycline hydrochloride) Soluble Powder (ANADA 200-374), filed by Cross Vetpharm Group Ltd. The ANADA provides for the use of tetracycline hydrochloride soluble powder in the drinking water of calves, swine, chickens, and turkeys for the treatment and control of various bacterial infections. For swine and calves, the product is indicated for the control and treatment of bacterial enteritis (scours) caused by *Escherichia coli* and bacterial pneumonia associated with *Actinobacillus pleuropneumoniae, Pasteurella* spp., and *Klebsiella* spp. sensitive to tetracycline hydrochloride. For chickens, the product is indicated for the control of chronic respiratory disease and air sac infection caused by *Mycoplasma gallisepticum* and *Escherichia coli* and infectious synovitis caused by *Mycoplasma synoviae* sensitive to tetracycline hydrochloride. For turkeys, the product is indicated for the control of infectious synovitis caused by *Mycoplasma synoviae* and bluecomb (transmissible enteritis, coronaviral enteritis) complicated by organisms susceptible to tetracycline hydrochloride. Cross Vetpharm Group Ltd.'s TETRAMED 324 HCA is approved as a generic copy of Boehringer Ingelheim Vetmedica, Inc.'s TETRASURE 324 (tetracycline hydrochloride), approved under NADA 65-496. Notice of approval was published November 7, 2005.

(Continued, next page)

Approvals for October 2005 – January 2006 *(Continued)*

Abbreviated New Animal Drug Applications (Continued)

HEIFERMAX 500 Liquid Premix (melengestrol acetate), RUMENSIN (monensin sodium), and TYLAN (tylosin tartrate) Type A medicated articles (ANADA 200-375), filed by Ivy Laboratories. The ANADA provides for use of melengestrol acetate Type A medicated article with monensin and tylosin Type A medicated articles to make three-way combination Type C medicated feeds for heifers fed in confinement for slaughter for increased rate of weight gain and improved feed efficiency, prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*, for suppression of estrus (heat), and reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces (Corynebacterium)* pyogenes. Ivy Laboratories' ANADA 200-375 is approved as a generic copy of Pharmacia & Upjohn's NADA 138-870. Notice of approval was published November 2, 2005.

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