FDA VETERINARIAN

Center for Veterinary Medicine

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CVM Issues ADUFA Performance Report for FY 04-05

The Center for Veterinary Medicine (CVM) confirmed in a recent report about its user fee program that the Center exceeded the performance goals set for Fiscal Year (FY) 2004 and, according to the data available at the end of that fiscal year, is exceeding its FY 2005 goals for those FY 2005 submissions reviewed and acted on as of September 30, 2005. Until all submissions in the FY 2005 receipt cohort (all applications submitted during FY 2005) are completed, only a preliminary performance assessment can be provided for that cohort.

Through the Animal Drug User Fee Act (ADUFA) of 2003, Congress authorized the Food and Drug Administration (FDA) to collect user fees to add resources to CVM's drug review process. At the same time, FDA agreed to meet certain deadlines for animal drug review. The deadlines require FDA to review and act on submissions within shorter periods of time each new year over the five-year life of the Act.

ADUFA also requires FDA to present Congress with annual performance reports following the close of a fiscal year. (The Federal fiscal year begins October 1 and ends September 30 of the following calendar year.)

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CVM Offers Several Lines of Communications for Constituents

by Dr. Charlotte Spires, Office of New Animal Drug Evaluation; Dr. Marcia Larkins, Ombudsman; Linda Grassie, Director, Communications Staff

The Center for Veterinary Medicine (CVM) of the Food and Drug Administration (FDA) works to educate animal health stakeholders and consumers, and to develop and disseminate information as it carries out its consumer protection mission.

CVM operates under and enforces applicable provisions of the Federal Food, Drug, and Cosmetic Act and other authorities. The Center is responsible for the evaluation, approval, and surveillance of animal drugs, food additives, feed ingredients, and marketed animal devices.

The Center has developed a variety of mechanisms for communicating with its constituencies to foster open and collegial partnerships, respond to stakeholder concerns, and to keep the public abreast of Center activities, so that the Center can better carry out its mission.

Here are some of the sources of information available to the public.

Website

The most comprehensive source for publicly available information about CVM of interest to the animal health community is CVM's website (*www.fda.gov/cvm*). It contains a variety of educational booklets and other information for free download.

The resources available on CVM's website include publications such as: the *FDA Veterinarian* newsletter (previous issues as well as this edition); CVM Updates, which are like press releases for the trade press; CVM Annual Reports; CVM Program Policy and Procedures Manual; a list of FDA Approved Animal Drugs in the "Green Book;" guidance documents; and other information and publications on issues of interest to veterinarians and animal owners, some in Spanish.

One of the major revisions to the CVM website this year was to the Adverse Drug Experience Reporting page (*www.fda.gov/cvm/adetoc.htm*).

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

CVM Offers Several Lines of Communications... *(Cont.)*

This page includes a Cumulative Adverse Drug Experiences Summaries Report, which is posted so that veterinarians and animal owners can have easy access to information about signs that have been associated with drugs (*www.fda.gov/cvm/ade_cum.htm*). At CVM, we encourage veterinarians to let us know about additional information they would like to see on our website. They can send their comments to the CVM Home Page at: CVMHomeP@cvm.fda.gov.

Electronic reading rooms

Certain 1996 amendments to the Freedom of Information (FOI) Act mandate publicly available electronic reading rooms with FOI response materials and other materials. The Freedom of Information Act (FOIA) was the first law to establish an effective legal right of access to government information, underscoring the crucial need in a democracy for open access to government information by citizens. A statement issued by President Clinton upon signing the 1996 FOIA amendments into law on October 2, 1996, said that the amendments apply to records maintained in an electronic format, and broadens public access to government information by placing more material on-line and expanding the role of the agency reading room.

Freedom of Information materials of interest to animal health stakeholders include FOI Summaries (of approved

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CVM Issues ADUFA Performance Report... *(Continued)*

All ADUFA review performance statistics are based on a fiscal year receipt cohort. This methodology calculates performance statistics for submissions for the fiscal year, in which FDA received them, regardless of when FDA ultimately acted on the submissions. A result of this approach is that the statistics shown for a particular year may change from one report to the next. As time passes, FDA completes work on more submissions in a receipt cohort. As more submissions are completed, the statistics for that year of receipt must be adjusted to reflect the new completions. Until all submissions in a cohort are completed, FDA can provide only a preliminary performance assessment for that cohort.

CVM's ADUFA performance goal is review at least 90 percent of a cohort of applications within the specified time frame.

The first ADUFA performance report FDA issued, released about a year ago, reported data available at the close of FY 2004. The more recent report (FDA's second, released in May 2006) contains complete performance data for FY 2004 cohort, and a preliminary performance report for FY 2005 based on data available on September 30, 2005.

Under ADUFA, CVM's goal is to complete 90 percent of applications within the time frame specified for the type of application.

Fiscal Year	*Deadline for review, number of days*	*Number of applications acted on*	*Number completed on time*	*On time percentage*
Original New Animal Drug Application (NADA), reactivations				
FY 2004	295	7	7	100%
FY 2005*	270	1	1	100%
Administrative NADAs, reactivations				
FY 2004	90	10	10	100%
FY 2005*	85	6	6	100%
Non-manufacturing supplemental NADAs, reactivations				
FY 2004	320	14	14	100%
FY 2005*	285	3	3	100%
Manufacturing supplemental NADAs, reactivations				
FY 2004	225	363	359	99%
FY 2005*	190	297	296	100%
Investigational New Animal Drug (INAD) studies				
FY 2004	320	243	243	100%
FY 2005*	285	162	162	100%
INAD study protocols				
FY 2004	125	173	172	99%
FY 2005*	100	148	147	99%

(*The FY 2005 figures are as of September 30, 2005.)

FDA VETERINARIAN

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CVM Offers Several Lines of Communications... *(Cont.)*

New Animal Drug Applications), animal drug environmental assessments, significant new animal drug approvals, Veterinary Master Files, Veterinary Medicine Advisory Committee information (such as transcripts), and information on other CVM regulatory activities. Many of these materials are posted on the CVM website at *www.fda.gov/cvm/efoi.html* and *www.fda.gov/cvm/vmactoc.htm*.

Communications Staff

CVM's Communications Staff provides information to individual constituents, manages the CVM website content, works with other FDA offices to provide information to the major media, provides information to the trade press, conducts outreach education activities, conducts the Center's Freedom of Information activities, and works with FDA Public Affairs Specialists throughout the United States (*www.fda.gov/ora/fed_state/dfsr_activities/dfsr_pas.html*) to provide information on CVM issues.

The Communications Staff also produces materials on CVM issues, such as booklets and videos on judicious use of antimicrobials in food producing animals (*www.fda.gov/cvm/JudUse.htm*), *FDA and the Veterinarian*, which provides information on FDA's jurisdiction and regulations, information for consumers and individuals who want to market products such as pet foods (*www.fda.gov/cvm/consumer.html*), an animation on antimicrobial resistance (*www.fda.gov/cvm/antiresistvideo.htm*), and a DVD which demonstrates CVM's method for detecting nitrofuran residues in shrimp.

The Communications Staff is currently working with veterinary associations to increase awareness about non-steroidal anti-inflammatory drugs (NSAID), particularly about the Client Information Sheets (CIS) that are included with every FDA-approved NSAID for oral use in dogs (see the article "What Veterinarians Should Tell Clients about Pain Control and Their Pets" in this issue).

Members of the public can call the Communications Staff, at 240-276-9300, for general information.

The Communications Staff also routinely answers questions sent to the CVM homepage. The Staff normally receives 15-30 e-mails through the homepage each week.

The Communications Staff can also help veterinarians and others find Center publications, approved animal drugs in the "Green Book," FOI Act summaries, Adverse Drug Experience summary reports, information on pet foods, and many other types of information.

The Communications Staff also helps veterinarians in contacting Center experts on particular topics for help with very specific or technical questions.

Ombudsman

One of CVM's official points of contact is its Ombudsman, Dr. Marcia Larkins. The Ombudsman's primary responsibility is dispute resolution related to regulated drug products. However, the Ombudsman also serves as a conduit to resources within CVM for answers to questions involving specific Center policies and procedures, general questions involving veterinary product jurisdiction issues, and general complaints or comments on current CVM science-based programs.

The Ombudsman's position is also an avenue you can use to offer suggestions on how policies, procedures, and guidance documents can be improved.

Communications to the Center

Most of the information sources listed above are ways for the public to obtain information from the Center. Conversely, the public may provide information to CVM through a number of mechanisms including the Ombudsman, public meetings, adverse (drug) event reporting, and petitions.

The public may express its viewpoint to CVM via several mechanisms including proposed rules, petitions, public meetings, and public hearings.

FDA will publish a notice of proposed rulemaking in the *Federal Register*. This notice describes the proposed

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CVM Information Sources

- CVM's website, *www.fda.gov/cvm*
- FDA Veterinarian newsletter, *www.fda.gov/cvm/fdavettoc.html*
- CVM UPDATES, *www.fda.gov/cvm/2006updates.htm*
- Annual reports, *www.fda.gov/cvm/cvmannualreports.htm*
- Program Policy and Procedures Manual, *www.fda.gov/cvm/FOI/ppindex.html*
- "Green Book," *www.fda.gov/cvm/Green_Book/greenbook.html*
- Guidance documents, *www.fda.gov/cvm/guidance.html*
- Spanish language publications, *www.fda.gov/cvm/CVMEspanol.htm*
- EFOIA, *www.fda.gov/cvm/efoi.html*
- CVM Veterinary Medicine Advisory Committee, *www.fda.gov/cvm/vmactoc.htm*

☎ Communications Staff phone: 240-276-9300

BSE INSPECTION UPDATE

CVM Reports BSE Inspection Figures as of April 29, 2006

As of April 29, 2006, the Food and Drug Administration (FDA) had received more than 44,000 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 re-inspect 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 April 29.)

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** – 266
- **Number of active firms handling materials prohibited from use in ruminant feed** – 175 (66 percent of those active firms inspected)

  Of those 175 firms:

  ❖ 2 (1.1 percent) was classified as OAI

(Continued, next page)

CVM Offers Several Lines of Communications... *(Continued)*

regulation and gives information on where to submit written comments.

Individuals or organizations may also petition the FDA to issue or change a regulation or to take some other action. Information on submitting petitions is found in Title 21 of the Code of Federal Regulations, Sections 10.30, 10.33, and 10.35.

FDA uses public meetings to discuss significant issues with the public and offer an opportunity for an exchange of ideas before the rulemaking process begins. Public hearings are an opportunity for the public to participate in a rulemaking proceeding. In a public hearing, the public can present testimony on issues included in an Agency proposal orally or in writing. Individuals or organizations must register to present orally at a hearing by submitting a written notice of participation to the Center.

Written comments for both public meetings and hearings are welcome at any time; however, the official record of a hearing will remain open to receive written comments for only a specified time period. Written comments are submitted to the FDA Dockets Management Branch. The addresses for sending comments on paper or electronically are always provided in a notice requesting the comments.

Public meetings and public hearings are open to everyone, although seating may be limited and free registration is required. These meetings are announced in the *Federal Register*, the *FDA Veterinarian*, and various trade publications.

(Dr. Spires will present a seminar at this year's American Veterinary Medical Association meeting about accessing information from CVM. At the seminar, she will explain the methods discussed in this article, and be able to answer any questions you have. The seminar is scheduled for July 19, 2006, 7:00-7:30 a.m., in room 325B of the Hawaii Convention Center.)

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

- ❖ 4 (2.3 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** – 1,092
- **Number of active firms handling materials prohibited from use in ruminant feed** – 430 (39 percent of those active firms inspected)

  Of those 430 firms:
  - ❖ 0 were classified as OAI
  - ❖ 5 (1.2 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** – 5,128
- **Number of active firms handling materials prohibited from use in ruminant feed** – 2,176 (42 percent of those active firms inspected)

  Of those 2,176 firms:
  - ❖ 0 were classified as OAI
  - ❖ 36 (1.7 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** – 162 (48 percent of those active firms inspected)

  Of those 162 firms:
  - ❖ 0 were classified as OAI
  - ❖ 3 (1.9 percent) were classified as VAI

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** – 6,558
- **Number of active renderers, feed mills, and protein blenders processing with prohibited materials** – 491 (7.5 percent of those active firms inspected)

  Of those 491 firms:
  - ❖ 2 (0.4 percent) were classified as OAI
  - ❖ 19 (3.9 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** – 14,627
- **Number of active firms handling materials prohibited from use in ruminant feed** – 4,314 (29 percent of those active firms inspected)

  Of those 4,314 firms:
  - ❖ 3 (0.1 percent) were classified as OAI
  - ❖ 117 (2.7 percent) were classified as VAI

Total firms

- **Number of active firms whose initial inspection has been reported to FDA** – 17,454
- **Number of active firms handling materials prohibited from use in ruminant feed** – 5,103 (29 percent of those active firms inspected)

  Of those 5,103 firms:
  - ❖ 5 (0.1 percent) were classified as OAI
  - ❖ 126 (2.5 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.)

Comings and Goings

New Hires

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Nina Kaplan, Biologist
- Veronica Taylor, Mathematical Statistician
- Matthew Lucia, Veterinary Medical Officer

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Christine Drobny, Management Specialist
- Rebecca Tollefson, Program Specialist
- Thomas Letonja, Veterinary Medical Officer

What Veterinarians Should Tell Clients About Pain Control and Their Pets

by Michele Sharkey, DVM, Office of New Animal Drug Evaluation; Margarita Brown, DVM, Office of Surveillance and Compliance; and Linda Wilmot, DVM, Office of New Animal Drug Evaluation

Non-steroidal anti-inflammatory drugs (NSAID) are commonly prescribed and extremely effective pain control drugs for pets. Like most drugs, they do cause side effects, some serious. Veterinarians are in the best position to inform their clients about these side effects, so the clients can take better care of their pets. And, pet owners expect veterinarians to explain all potential risks of medications.

Dogs are living longer and healthier lives thanks to advances in veterinary medicine and pharmaceuticals. With active lifestyles that extend into advanced ages, dogs are often diagnosed with osteoarthritis or undergo surgical procedures and are treated for post-operative pain. NSAIDs are among the most common analgesics prescribed in these cases.

NSAIDs are used to control signs of arthritis, including inflammation, swelling, stiffness, and joint pain. Inflammation—the body's response to irritation or injury—is characterized by redness, warmth, swelling, and pain. NSAIDs work by blocking the production of prostaglandins, the body chemicals that cause inflammation.

In the United States, NSAIDs commonly used in dogs include ETOGESIC (etodolac), RIMADYL (carprofen), METACAM (meloxicam), ZUBRIN (tepoxalin), DERAMAXX (deracoxib), PREVICOX (firocoxib), and NOVOX (generic carprofen). These drugs have been approved by the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) for use in dogs. (You can get more information about these drugs by going to CVM's website, *www.fda.gov/cvm*. Once there, go to the "Green Book" navigational button, where you can look up the drugs by their brand names or active ingredient.)

Other NSAIDs are available in the United States for human uses, but have not been approved for use in dogs. (In the United States, there are no oral NSAIDs approved for use in cats.) Sometimes there may not be an approved animal drug available for a specific indication or dosage form. However, the Animal Medicinal Drug Use Clarification Act of 1994 gives veterinarians the same kind of discretionary authority available to physicians, allowing veterinarians to prescribe drugs for "extralabel" uses, which are uses not listed on the label.

As they should with any medication, veterinarians should discuss the benefits as well as the risks of the drugs with their clients when prescribing an NSAID. Every year millions of doses of medications are prescribed for dogs with good reason—but many adverse reactions occur. Most adverse reactions are mild, but some result in permanent impairment or even death. If the client can recognize a possible reaction and stop the medication while seeking veterinary attention for the dog, the client may make the difference between a good outcome and a disaster.

The most common side effects from NSAIDs include vomiting, loss of appetite, depression/lethargy, and diarrhea. Some side effects can be serious, especially if the drug is not used according to labeled directions, resulting in the need for medical care. Serious adverse reactions include gastric ulcers, kidney and liver problems. Death may result in some instances.

All NSAIDs approved for oral use in dogs come with a Client Information Sheet (also known as the Information for Dog Owner Sheet) that describes the drug's side effects. Dog owners should ask veterinarians for the Client Information Sheet when an NSAID is prescribed. These Client Information Sheets provide the dog owner with important information in a user-friendly manner regarding what can be expected from use of the drug and what side effects to look for.

Not all side effects can be predicted

All approved medications indicated for pets are subject to extensive evaluation by a drug company using stringent standards set by the CVM before they are marketed. Every effort is made to ensure safe and effective treatments. However, every drug has the potential for side effects. Pre-testing by the animal drug manufacturer and review of the data from those tests by the government ensure that the animal drug is safe and effective. Because of the relatively low frequency of some adverse events, some adverse effects are recognized only after the marketing of the product in a large population of animals.

NSAID therapy can also unmask hidden disease, previously undiagnosed due to the absence of apparent clinical signs. Dogs with underlying kidney disease, for example, may experience worsening of that disease while on NSAIDs. Dogs at greatest risk for kidney problems are those that are dehydrated, on concomitant diuretic therapy, or have kidney, heart, and/or liver dysfunction.

Unexpected reactions to a drug are reported to the drug manufacturer, and every reaction reported to a pharmaceutical manufacturer must by law be reported to the FDA.

Advice given to owners

We recommend that pet owners work with their veterinarians to make medication decisions including using

(Continued, next page)

What Veterinarians Should Tell... *(Continued)*

over-the-counter drugs, vitamins, herbal supplements, flea control products, and other medications. Giving medications and other over-the-counter products at the same time could be detrimental to a dog's health.

Many reactions due to NSAIDs may be lessened if owners are aware of potential side effects, and with appropriate use many can be minimized or avoided. First and foremost, if an owner suspects a reaction to an NSAID, the owner should stop administering the drug immediately and should contact a veterinarian. Some reactions are mild and go away after stopping the drug.

The veterinarian is in the best position to advise the dog owner on using an NSAID. Before administering an NSAID to a dog, the veterinarian often recommends blood tests. The knowledge gained from these tests could be critical in deciding if the drug is safe to use in a dog. If a dog is prescribed an NSAID for the control of pain associated with osteoarthritis, regular veterinarian check-ups and blood tests are recommended to evaluate the continued use of the drug.

When treating a dog with an NSAID, the owner should never increase the dose or frequency of administration. The owners should follow their veterinarians' instructions.

A pet owner should never give an NSAID to a dog unless under the direction of a veterinarian.

Pain control in response to the use of an NSAID varies between dogs (just as it does in people). Because the response to pain medication is individualized, no one NSAID is considered more effective than another, and because every NSAID can cause adverse reactions, including stomach/intestinal ulcers and death, none is considered safer than others.

But selecting the best NSAID is important. With advances in the recognition and definition of animal pain and the many NSAID choices available, much benefit can be gained from the appropriate and careful use of these drugs.

Sometimes, the process of finding the best NSAID can mean changing the prescription. Only one brand of NSAID should be administered to a dog at any given time. If at some time the owner and the veterinarian decide to try a different NSAID, a wash-out period is recommended. A wash-out period is a few days long, during which the dog does not receive any NSAID. Then the dog can be switched to another NSAID. NSAIDs should not be combined with the use of a corticosteroid, either.

The pain associated with osteoarthritis waxes and wanes, and drugs used to control this pain should only be administered when necessary. If the dog seems to improve to the point of not needing the drug, the owner should discuss continued use of the NSAID with a veterinarian.

The key to making any transition or change work well is good veterinarian-client communications.

An informed dog owner is the best defense against serious side effects from NSAIDs. The veterinarian is the most qualified source for information regarding NSAID use and a dog's care. Owners should not hesitate to ask questions and inquire about possible side effects or signs to watch for when treating a dog. A Client Information Sheet, which a veterinarian should give the pet owner whenever an NSAID is prescribed, serves as a reminder of this information for use at home.

What starts out as a minor problem can readily progress to an emergency. An owner should be encouraged to call his or her veterinarian with any concerns about the NSAID the dog is receiving. The veterinarian and/or owner may even call the drug manufacturer (a toll free number appears on each label and the Client Information Sheet). Pharmaceutical companies offer customer service and technical support for product information and quality control. When possible problems are experienced with a product, the manufacturer may have specific recommendations for the treating veterinarian regarding tests and treatments.

Advice to Dog Owners Whose Pets Take NSAIDs

by Michele Sharkey, DVM, Office of New Animal Drug Evaluation; Margarita Brown, DVM, Office of Surveillance and Compliance; and Linda Wilmot, DVM, Office of New Animal Drug Evaluation

Non-steroidal anti-inflammatory drugs (NSAID) have provided pain control for many dogs and offer significant benefits. But it is important that you are aware of potential side effects when administering drugs to your dog. All NSAIDs should be used with caution, because they all have the potential for serious side effects, especially gastrointestinal bleeding, ulcers, perforations, even in rare cases kidney damage and liver problems.

The best way to avoid the possibility of your dog suffering serious side effects from NSAIDs is for you

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Advice to Dog Owners... *(Continued)*

to be fully informed about the drug and its potential side effects.

NSAIDs approved for use in dogs contain the following information on their labels:

All dogs should undergo a thorough history and physical examination before initiation of NSAID therapy. Appropriate laboratory tests to establish baseline blood values prior to, and periodically during, the use of any NSAID are strongly recommended.

As an owner, you should receive a Client Information Sheet with every NSAID prescription. You should ask your veterinarian for this sheet if you do not receive one. One way to be better informed is to read this information carefully before administering the medication to your dog, so that you understand the side effects that your dog may experience.

When administering an NSAID, you should watch for these side effects:

- Decrease or increase in appetite
- Vomiting
- Change in bowel movements (such as diarrhea, or black, tarry, or bloody stools)
- Change in behavior (such as decreased or increased activity level, incoordination, seizure or aggression)
- Yellowing of gums, skin, or whites of the eyes (jaundice)
- Change in drinking habits (frequency, amount consumed)
- Change in urination habits (frequency, color, or smell)
- Change in skin (redness, scabs, or scratching)

If you notice any of these possible side effects, stop the medication and contact your veterinarian.

The side effects listed on the label are the most common. All possible side effects are not included. Always contact your veterinarian if you have questions about your dog's medication.

What starts out as a minor problem can readily progress to an emergency. If you feel that your concerns are not taken seriously, you should get another opinion. You may even call the drug manufacturer (a toll free number appears on each Client Information Sheet). Pharmaceutical companies offer customer service and technical support for product information and quality control. When possible problems are experienced with a product, the manufacturer may have specific recommendations for your veterinarian regarding tests and treatments.

Reporting adverse drug experiences

If you or your veterinarian suspect a potential reaction associated with the use of an NSAID (or any drug), report it to the pharmaceutical company. All NSAIDs approved for use in dogs have a toll free number on their labels to which a suspected reaction can be reported. If unable to report problems directly to the pharmaceutical company, veterinarians and dog owners are encouraged to report veterinary Adverse Drug Experiences (ADE) and suspected product failures to the government agency that regulates the product in question. In the case of NSAIDs, the adverse experiences are to be reported to the Center for Veterinary Medicine.

Questions regarding ADE Reporting should be addressed to:

Center for Veterinary Medicine
Division of Surveillance, HFV-210
7519 Standish Place
Rockville, MD 20855
1-888-FDA-VETS

With this information in hand, you are now equipped to advocate for your dog in order to assure that he or she receives the best care possible. Take the time to be your "dog's best friend."

The Review of Animal Production Drugs by FDA

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

When we consider drugs used in animals, we typically think of therapeutic drugs, which, according to the Federal Food, Drug, and Cosmetic Act (FD&C Act), are intended to "diagnose, cure, mitigate, treat, or prevent disease in animals." However, the FD&C Act also defines a different category of animal drugs as "articles, other than food, intended to affect the structure or function of the body of an animal." This category includes products known as animal production drugs.

Animal production drugs are administered to animals to enhance the production of edible or non-edible products or to increase the efficiency of a particular

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The Review of Animal Production Drugs... *(Cont.)*

phase of life, including reproduction. Similar to therapeutic animal drugs, animal production drugs must be approved by the Food and Drug Administration (FDA) before they can be used commercially in the United States. By approving animal production drugs, FDA provides livestock producers safe and effective products to improve the productive capabilities of animals on U.S. farms.

Animal production drugs are unique

Animal production drugs are intended for use in healthy animals. Livestock for which production drugs have been approved in the United States include beef and dairy cattle, swine, poultry, and sheep. The products are intended to improve physiological endpoints of importance to the producer. Examples of claims for production drugs approved in the United States include increased rate of weight gain, improved feed efficiency, increased production of saleable milk, increased carcass leanness, and synchronization of estrus.

Most animal production drugs are approved for over-the-counter use. Thus, instructions and information on the label must be clear and complete so that a lay person can use the drug safely. Extralabel use of animal production drugs generally is not allowed.

Review of animal production drugs by FDA

FDA's Center for Veterinary Medicine (CVM) reviews new animal drugs in the Office of New Animal Drug Evaluation (ONADE). Within ONADE, the Division of Production Drugs is primarily responsible for the review of new animal production drugs. Other Divisions and Teams within ONADE support the review, including the Division of Human Food Safety, Division of Manufacturing Technologies, the Biometrics Team, and the Environmental Safety Team.

Before a new animal drug receives FDA approval, a sponsor must show that it is safe and effective. Safety covers three areas: human, animal, and environmental. Most animal production drugs are intended for food-producing animals. Thus, a drug sponsor must test the edible products from treated animals (e.g., meat, milk, and eggs) for safety to human consumers and demonstrate that edible products are free of unsafe drug residues. In addition, sponsors determine the safety of the drug to people handling and administering it to animals. Sponsors must show that a new animal drug is safe to the treated animal. They also determine the impact of the production and use of the drug on the environment. Effectiveness means that the drug does what the sponsor claims, e.g., increases rate of weight gain. In addition to demonstrating safety and effectiveness, a sponsor must demonstrate its ability to manufacture the drug product to a consistent potency and purity.

The FD&C Act does not address the "societal need" for an animal drug or the drug's economic impact. Therefore, by law, FDA cannot consider these issues when deciding whether to approve a new animal drug. Once FDA determines that an animal drug is safe and effective, the U.S. marketplace tends to decide these elements.

Investigational use of new animal drugs

The drug sponsor conducts studies to evaluate the safety and effectiveness of a new animal drug, as well as the sponsor's capability to manufacture the animal drug. The sponsor also develops analytical methods to detect and measure drug residues in edible animal products.

Unapproved drugs are illegal to use. However, a drug sponsor is permitted to conduct investigational studies using an unapproved new animal drug so long as the sponsor complies with applicable investigational regulations found at 21 CFR (Code of Federal Regulations) Part 511. A sponsor notifies CVM of shipment/delivery of the drug for clinical investigations by submitting to an Investigational New Animal Drug file (INAD) a notice of shipment, which includes information such as the location of studies, number of animals treated, doses, and duration of treatment. A sponsor may also request authorization to market food from the large number of investigational animals typically needed to evaluate the safety and effectiveness of a new animal production drug. CVM will authorize the use of the food products of investigational animals only if the food products are determined to be safe for human consumption.

CVM oversight

CVM oversees a sponsor's investigational activities with a new animal drug in several ways. Although not required, most sponsors typically submit protocols of their proposed safety and effectiveness studies for CVM scientists to review before conducting the studies. CVM scientists provide recommendations on factors such as study design, animal numbers, management of study animals, variables to be measured, and proper statistical analysis. This input increases the likelihood that a study will provide the data needed by CVM to determine if the drug is approvable.

FDA has developed standards by which safety studies are to be conducted. These are known as the Good Laboratory Procedures (GLP). In addition, CVM has developed standards for clinical animal studies (typically the effectiveness study), called Good Clinical

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The Review of Animal Production Drugs... *(Cont.)*

Practices (GCP). These standards address issues such as appropriate expertise and responsibilities of study personnel, the need for quality assurance procedures, general study design, procedures to reduce potential bias in results, and study documentation. By following the GLP and GCP standards, drug sponsors improve the accuracy, integrity, and correctness of data from their safety and effectiveness studies.

FDA has a Bioresearch Monitoring Program by which CVM scientists inspect safety and effectiveness studies of animal drugs while they are conducted. This program provides CVM scientists firsthand information on conduct of the study, health and appearance of study animals, and quality of data collection.

Once safety and effectiveness studies are completed, sponsors submit not only summary reports to CVM, but all the data collected during the studies. CVM scientists examine the data to ensure that all study animals are accounted for and were properly managed. They also examine whether there were problems such as extensive missing data and/or biologically unusual results. These factors help CVM scientists determine whether a study is acceptable to evaluate the safety and/or effectiveness of the drug. In addition, CVM statisticians determine whether the data were properly summarized and analyzed.

Evaluating the effectiveness of new animal production drugs

Effectiveness studies of new animal production drugs are well-controlled studies designed to determine whether the product achieves its proposed claims under expected use conditions. The effectiveness study may also contribute information regarding the drug's safety and information for product labeling that is helpful to the potential user of the drug.

Drug sponsors will typically choose study locations that are major production areas in the United States for the species/class of animal and type of production being evaluated. Research or commercial farms may be used. A sufficient number of normal, healthy animals representative of their production class are assigned to the study to provide adequate statistical power to evaluate the proposed claims.

The new animal production drug is administered to study animals as it is intended to be used. For example, the drug might be administered in the feed, injected, or implanted under the skin. If a sponsor is seeking approval of a single dose of the new animal production drug, treatment groups will consist of the intended dose and an appropriate control group. The sponsor may instead choose to seek approval of a dose range, in which case several doses will be included in the study in addition to a control group. Treatment and control group assignments are concealed from study personnel so that all study animals are handled in a consistent manner throughout the study to minimize bias.

Effectiveness studies for new animal production drugs are conducted until animals are marketable, for an appropriate portion of the production cycle, or for a period of time sufficient to determine the effect on a reproductive claim. For example, for claims associated with meat production, treatment will usually be conducted until animals reach a terminal weight (slaughter or market). For dairy production claims, treatment will usually encompass at least a complete lactation cycle and a portion of the subsequent lactation.

Effectiveness studies for new animal production drugs incorporate common U.S. commercial management practices for the species and class of animal and study location, such as housing and feeding, while maintaining a well-controlled study. Invasive measures, such as routine blood collection, are usually avoided during the effectiveness study, so as not to affect the response of the study animals to treatment.

In addition to measuring data associated with the claims of interest, other production variables or animal product quality may be measured. For example, for a production drug intended to increase carcass leanness, economically important factors such as weight gain, feed efficiency, or meat quality may be measured to determine if there are any negative effects.

The safety of a new animal production drug to the treated animal is determined in part from non-clinical target animal safety studies. However, effectiveness studies for new animal production drugs also provide considerable information on the effects of the drug on animal health. The large number of animals often used in effectiveness studies provides power to detect low frequency adverse events. Effectiveness studies also provide information on the health of animals treated with the production drug under conditions similar to commercial practices. Thus, all animals in an effectiveness study should be observed at least daily for all signs of illness, such as reduced feed intake, lameness, abnormal respiration, reproductive abnormalities, mastitis, or injuries. Necropsies are performed on all animals that die or are euthanized.

Approval of a new animal production drug

CVM scientists first determine if studies conducted and submitted by the sponsor to evaluate the safety and effectiveness of a new animal production drug are acceptable and that data were properly summarized and statistically analyzed. Once these initial determinations have been made, CVM scientists will review all results and determine if the drug is safe and effective.

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The Review of Animal Production Drugs... *(Cont.)*

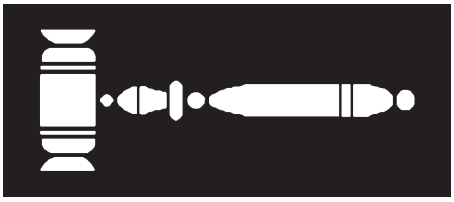
CVM may determine that a new animal production drug is not safe and/or effective or that more data are needed to reach conclusions about it. More specifically, CVM scientists will determine not only if the proposed claim (for example, increased rate of weight gain) is statistically significantly improved by treatment with the new animal production drug, but also whether the amount of the improvement is biologically meaningful (in terms of livestock production). Similarly, CVM scientists will examine the effect of the drug on other production and animal health variables that were measured during the study to determine if there were any negative effects associated with use of the production drug. If any adverse reactions are severe, it may be determined that the drug is not safe.

The labeling on an approved drug communicates important information gathered from the safety and effectiveness studies. Once a new animal drug is determined to be approvable, CVM scientists will review proposed product labeling to make sure that it accurately describes the approved claim and clearly describes how to properly use the drug. This information includes any withdrawal period necessary before food products from treated animals may be used for human consumption. Product labeling also includes information on adverse effects that might be increased in treated animals but that are not so severe to prevent approval of the product, plus any approaches to minimize these risks. To further describe the basis for deciding that the drug is safe and effective, CVM also makes available to the public a Freedom of Information Summary.

Conclusion

The FDA's thorough review of new animal production drugs ensures that only safe and effective products are available to U.S. livestock producers. These products in turn provide livestock producers safe and effective approaches to improve the productive capabilities of animals on their farms and help to ensure a plentiful food supply.

Regulatory Activities



The following individuals and firms received Warning Letters for offering animals for slaughter as food that were adulterated because of the presence of illegal tissue residues:

- Daniel J. Petrie, owner, Petrie Farms, Arcade, NY
- William Boman, Susquehanna, PA
- Ronald A. Lamarche and Yvette Lamarche, owners, Windy Ridge Farm, Charleston, ME
- Pete Tuls and Brian Hemann, co-owners, Lost Trail Dairy, LLC, Liberal, KS

Animals at these facilities were held under conditions that were so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply. For example, each operation lacked an adequate system to ensure that animals medicated by the operation were withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues. In addition, new animal drugs were adulterated when each of the operations failed to use a drug in conformance with its 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 extralabel use of approved veterinary or human drugs must comply with sections 512(a)(4) and 512(a)(5) of the Federal Food, Drug, and Cosmetic Act (the Act) and 21 CFR Part 530. FDA investigations found that the extralabel use of new animal drugs at these operations failed to comply with these requirements and resulted in illegal drug residues. Because the extralabel use of the drugs was not in compliance with Part 530, the drugs were caused to be unsafe and adulterated. The above violations involved Penicillin G Procaine Injectable Suspension, Flunixin Meglumine, Dihydrostreptomycin Sulfate, and Sulfamethazine in dairy cows.

A Warning Letter was issued to Joseph Valentine, Union Dale, PA, because an investigation of Mr. Valentine's dairy operation revealed that he offered an animal for sale for slaughter as food that was adulterated because of the presence of illegal tissue residues. The investigation also found that animals were held under conditions that are so inadequate that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. The operation lacks an adequate system to ensure that animals medicated by the facility are withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues.

A Warning Letter was issued to Stephen J. Palladino, partner, Hardie Farms, Inc., Lansing, NY, because an investigation of the dairy operation confirmed that the new animal drug Agri-cillin Procaine Penicillin G was caused to become adulterated. Specifically, the illegal extralabel use of the drug rendered

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Regulatory Activities *(Continued)*

the drug unsafe and, therefore, adulterated. The dairy operation treated a dairy cow with the drug in a manner contrary to the drug's approved labeling. Extralabel use 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. Agri-cillin was administered to a dairy cow in an extralabel manner, without following the daily dosage level, duration of treatment, or dosage level per injection site requirements set forth in the approved labeling, and was done without the supervision of a licensed veterinarian.

A Warning Letter was issued to Chris P. Hytrek, DVM, owner, Willow Creek Veterinary Service, Cortland, NE, because an investigation of his veterinary practice revealed that Dr. Hytrek caused animal drugs used in his practice to be unsafe and adulterated because they were used in a manner that did not conform with their approved use or the regulations for Extralabel Drug Use in Animals, 21 CFR Part 530. The investigation revealed that Dr. Hytrek prescribed the drugs kanamycin and amikacin to Wil Mar Sen Dairy. A U.S. Department of Agriculture analysis of tissue samples identified the presence of these two drugs in the kidney tissue of a cow offered for sale for slaughter as food from Wil Mar Sen Dairy. Neither kanamycin nor amikacin is approved for use in cattle. No tolerance levels have been established for these drugs in edible tissues from cattle. The detectable presence of kanamycin and amikacin in the edible tissues of the animal caused the food to be adulterated. The extralabel use of approved veterinary or human drugs is permitted only if it complies with the Act and 21 CFR Part 530. Dr. Hytrek failed to comply in that he did not establish substantially extended withdrawal periods supported by appropriate scientific information for the extralabel use of these two drugs in food producing animals; he failed to institute procedures to assure that the identity of treated animals was carefully maintained; and he did not take appropriate measures to ensure that there were no illegal residues in the dairy cows for which he prescribed the extralabel use of kanamycin and amikacin.

A Warning Letter was issued to Donald R. Pilegard, president, Jensen & Pilegard, Fresno, CA, because an investigation of the licensed medicated feed mill found significant deviations from the current Good Manufacturing Practice (cGMP) regulations for medicated feeds. Such deviations cause feeds manufactured at this facility to be adulterated under of the Act. In addition, the investigation revealed deviations from labeling requirements that cause the medicated feeds manufactured at this facility to be misbranded. The deviations from the label requirements also cause the medicated feed to be unsafe and, therefore adulterated. The following deviations from cGMP requirements were found:

(1) Failure to have adequate cleanout procedures for all equipment used in the manufacture and distribution of medicated feeds to avoid unsafe contamination of feed with drugs;
(2) Failure to maintain a Master Record File, which includes the correct name of each drug ingredient to be used in the manufacture of the medicated feed. In addition, the Master Record File had not been prepared, checked, dated, and signed or initialed by a qualified person;
(3) Failure to maintain a Master Record File, which includes a copy or description of the label or labeling that will accompany the medicated feed;
(4) Failure to accurately test all scales used in the manufacture of medicated feeds at least once per year or more frequently as may be necessary to insure their accuracy; and
(5) Failure to have suitable construction to minimize access by rodents, birds, insects, and other pests, to maintain the building in a reasonably clean and orderly manner, and to maintain the building grounds so that they are reasonably free from waste and refuse.

The medicated feeds were misbranded due to the mill's practice of using a page from the *Feed Additive Compendium* as labeling. This practice does not provide sufficient information to allow the purchaser of the medicated feed to use the feed in a safe manner. In addition, there are serious concerns over the mill's drug inventory and reconciliation practices. Specifically, the mill has a practice of rounding drug usage amounts up or down to simplify calculations and had failed to take corrective action to reconcile drug discrepancies and accurately weigh drug ingredients. FDA's regulations require that drug inventory be maintained by means of a daily comparison of the actual amount of drug used with the theoretical drug usage and to investigate any significant discrepancy and take corrective action.

A Warning Letter was issued to Raymond Kastendieck, president, FRM Chemical, Inc., Washington, MO, because inspections of the animal drug manufacturing facility found significant deviations from the cGMP regulations for finished pharmaceuticals. Such deviations cause animal drug products manufactured at this facility to be adulterated under the Act. The investigation found the following deviations:

(1) Failure to perform at least one specific identity test on each drug component received, in lieu of testing each component for conformity with all appropriate written specifications for purity, strength, and quality;
(2) Failure to establish and follow a written program for calibration of instruments, apparatus, gauges, and recording devices used to assure that drug products conform to appropriate standards of identity, strength, quality, and purity;
(3) Failure to conduct cGMP training on a continuing basis;
(4) Failure to establish written procedures describing the in-process controls and tests, or examinations to be conducted on appropriate samples of in-process controls and tests, or examinations to be conducted with appropriate samples of in-process materials of each batch;
(5) Failure to establish written procedures designed to prevent

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Regulatory Activities *(Continued)*

objectionable microorganisms in drug products;
(6) Failure to establish written control procedures for the issuance of labeling;
(7) Failure to establish written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; and
(8) Failure to establish written procedures for evaluation, at least annually, of the quality standards of each drug product.

Warning Letters were issued to Herbert B. Tully, president, Wilbur Ellis Company, San Francisco, CA, regarding the company's licensed medicated feed mill known as Knox McDaniel Company in Ogden, UT, and to Bryan K. Draper, owner, Western Ag Industries, Genola, UT, regarding the company's medicated feed distribution business because investigations of both establishments revealed that on several occasions they sold a Category II, Type A medicated article (Amprolium 25%) to a firm that does not have a Medicated Feed Mill License. A new animal drug is deemed unsafe, and, therefore, adulterated if it is removed from a distributor's establishment for use in the manufacture of animal feed, unless at the time of such removal the distributor has an unrevoked written statement from the consignee of the drug, or notice from the Secretary of the Health and Human Services, to the effect that, with respect to the use of such drug in animal feed, such consignee (1) holds a license issued under section 512(m) [21 U.S.C. § 360(m)] and possesses current approved labeling for such drug in animal feed, or (2) will, if the consignee is not a user of the drug, ship such drug only to a holder of a license issued under 512(m) [21 U.S.C. § 360(m)]. The firms had no such written statement on file from the feed mills to which the Amprolium 25% was sold. In addition, Western Ag Industries' own-label medicated feed "Western Ag Industries Amprolium Crumbles" is being manufactured by a firm without a Medicated Feed Mill License, and is unsafe under the Act, and therefore, adulterated.

A Warning Letter was issued to Greta Armstrong, Risingsun Health Alternatives and Herbs, Division of McAdam Health Enterprises, Livingston, MT, concerning products marketed on its Internet websites. One of the products, Bla-Cansema Type Black Salve For Pets, is intended for use in cats and dogs; the other products are intended for use in humans. According to the websites, the salves, capsules, and tonics are sold as topical and oral treatments for various forms of cancers, heart disease, high blood pressure, diabetes, and numerous other life threatening diseases. Ordering instructions and a price list for the products are provided on the website. Consumers are directed to select the desired products and are provided with a secure payment processor to facilitate payment by credit card to Risingsun Health Alternatives. Based on the claims cited, the products are "drugs" as defined by 21 U.S.C. § 321(g). Moreover, all the products are either "new drugs" or "new animal drugs" as defined by 21 U.S.C. § 321(p) and 21 U.S.C. § 321(v), respectively, because there is no evidence that they are generally recognized as safe and effective for the intended uses conveyed in their labeling. Furthermore, the salves are topical products and cannot be dietary supplements because they are not intended for ingestion, but rather to bypass the alimentary canal by direct absorption through the skin. The Act defines the term "dietary supplement" to mean a product that is "intended for ingestion…." Consequently, topical products intended to enter the body directly through the skin or mucosal tissues are not "dietary supplements." For these products, both disease and structure/function claims cause them to be new drugs. Under 21 U.S.C. § 355(a), a "new drug" may not be introduced or delivered for introduction into interstate commerce unless an FDA-approved drug application is in effect for the drug. The distribution of the products intended for humans are in violation of 21 U.S.C. § 355 and prohibited by 21 U.S.C. § 331(d). The Bla-Cansema Type Black Salve For Pets is adulterated under 21 U.S.C. § 351(a)(5), because it is unsafe under 21 CFR U.S.C. § 360b, because it is a new animal drug, and there is no FDA-approved new animal drug application in effect for the drug.

A Warning Letter was issued to Gary Schell, president, Schell and Kampeter, Inc., Meta, MO, because an inspection of the company's pet food manufacturing facility located in Gaston, SC, revealed significant deviations from the Act. The investigation determined that the facility manufactures various dog and cat food products under several labels including Diamond, Country Value, and Professional. The FDA investigator documented that the facility manufactured a number of lots of dog food between September 1 and November 30, 2005, which were released for distribution in interstate commerce, that were adulterated under section 402(a)(1) of the Act [21 U.S.C. § 342(a)(1)] because they contained a poisonous or deleterious substance (aflatoxin), which may render them injurious to health. In addition, these lots of pet food were adulterated under section 402(a)(4) [21 U.S.C. § 342(a)(4)]. The inspection revealed that the facility failed to implement appropriate controls to prevent the adulteration of the pet food, and that the plant personnel failed to follow established procedures, which, if followed, could have prevented these violative lots from being distributed. The inspection also revealed that the waste or salvaged materials from pet food production (scrapes) were being sold to a local hog farmer in bulk. Some of the pet food manufactured at the plant contains protein derived from mammalian tissues. The scrape product, which may contain prohibited material, was not labeled with the statement "Do not feed to cattle or other ruminants" as required by 21 CFR 589.2000. This regulation is intended to help prevent the establishment and amplification of Bovine Spongiform Encephalopathy (BSE). This labeling deviation causes the distributed pet food scrapes to be misbranded within the meaning of section 403(a)(1) [21 U.S.C. § 343(a)(1)] of the Act.

Approvals for March and April 2006

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

POULTRYSULFA (sulfamerazine, sulfamethazine, and sulfaquinoxaline) Antimicrobial Soluble Powder (NADA 100-094), filed by Alpharma, Inc. The NADA provides revised labeling for an over-the-counter soluble powder containing sulfamerazine, sulfamethazine, and sulfaquinoxaline used in drinking water of chickens and turkeys as an aid in the control of coccidiosis and acute fowl cholera. The NADA relies on the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group's (DESI) effectiveness evaluation and subsequent Food and Drug Administration (FDA) conclusions. The findings were published in the *Federal Register* of July 5, 1984 (49 FR 27543). Using the official analytical method of detection, residues of sulfamethazine and sulfamerazine in edible tissues co-elute and cannot be quantified individually. There are no products containing only sulfamerazine approved for use in chickens or turkeys. Therefore, a tolerance for sulfamerazine residues in edible tissues of chickens or turkeys is not established at this time. Products that comply with the NAS/NRC findings and FDA's conclusions regarding those findings are eligible for immediate copying under the Generic Animal Drug and Patent Term Restoration Act (GADPTRA) (see the eighth in a series of policy letters issued to facilitate implementation of GADPTRA that published in the *Federal Register* of August 21, 1991 [56 FR 41561]) and is available online at *www.fda.gov/cvm/Documents/8thltr.doc*. Notice of approval of NADA 100-094 was published March 14, 2006.

BOVATEC (lasalocid sodium) and AUREOMYCIN (chlortetracycline) Type A medicated articles to formulate two-way combination drug Type B and Type C medicated feeds (NADA 141-250), filed by Alpharma, Inc. The NADA provides for use of approved single-ingredient Type A medicated articles containing lasalocid and chlortetracycline to formulate two-way combination drug Type B and Type C medicated feeds for pasture cattle and cattle fed in confinement for slaughter. Notice of approval was published April 27, 2006.

CVM has published in the *Federal Register* notice of the approval of these Supplemental NADAs

SAFE-GUARD (fenbendazole) Canine (NADA 121-473), filed by Intervet, Inc. The supplemental NADA provides for minor changes to the labeling of over-the-counter fenbendazole orally administered granules used for the treatment and control of certain internal parasites in dogs. The drug is indicated for use in adult dogs and puppies, six weeks of age or older, for the treatment and control of roundworms (*Toxocara canis, Toxascaris leonina*), hookworms (*Ancylostoma caninum, Uncinaria stenocephala*), whipworms (*Trichuris vulpis*), and tapeworms (*Taenia pisiformis*). Notice of approval was published April 14, 2006.

PENNCHLOR (chlortetracycline) Type A medicated articles (NADA 138-935), filed by Pennfield Oil Co. The supplemental NADA provides for a 0-day withdrawal time before slaughter when Type C medicated feeds containing chlortetracycline are fed to cattle. PENNCHLOR (chlortetracycline) Type A medicated article is used for making medicated

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Approvals for March and April 2006 *(Continued)*

Supplemental NADAs (Continued)

feeds for the treatment of various bacterial diseases of livestock. It is indicated in beef cattle for the control of bacterial pneumonia associated with shipping fever complex caused by *Pasteurella* spp. susceptible to chlortetracycline; in beef cattle (under 700 lbs.) for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline; for beef cattle (over 700 lbs.) for control of active infection of anaplasmosis caused by *Anaplasma marginale* susceptible to chlortetracycline; for calves, beef, and nonlactating dairy cattle for treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline; for breeding sheep for reducing the incidence of (vibrionic) abortion caused by *Campylobacter fetus* infection susceptible to chlortetracycline; for swine for reducing the incidence of cervical lymphadenitis (jowl abscesses) caused by *Group E Streptococci* susceptible to chlortetracycline; for breeding swine for the control of leptospirosis (reducing the instances of abortions and shedding of leptospirae) caused by *Leptospira pomona* susceptible to chlortetracycline; for swine for treatment of bacterial enteritis caused by *Escherichia coli* and *Salmonella cholerasuis*, and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline; for chickens for control of infectious synovitis caused by *Mycoplasma synoviae* susceptible to chlortetracycline; for chickens for control of chronic respiratory disease (CRD) and air sac infection caused by *Mycoplasma gallisepticum* and *Escherichia coli* susceptible to chlortetracycline; for chickens for reduction of mortality due to *Escherichia coli* infections susceptible to chlortetracycline; for turkeys for control of infectious synovitis caused by *Mycoplasma synoviae* susceptible to chlortetracycline; for turkeys for control of hexamitiasis caused by *Hexamita meleagrides* susceptible to chlortetracycline; for turkey poults not over 4 weeks of age for reduction of mortality due to paratyphoid caused by *Salmonella typhimurium* susceptible to chlortetracycline; and for turkeys for control of complicating bacterial organisms associated with bluecomb (transmissible enteritis, coronaviral enteritis) susceptible to chlortetracycline. Notice of approval was published April 7, 2006.

ORBAX (orbifloxacin) Tablets (NADA 141-081), filed by Schering-Plough Animal Health Corp. The supplemental NADA provides for revised animal safety labeling for orbifloxacin tablets used in dogs and cats for the management of diseases associated with susceptible bacteria. Specifically, the revisions include the addition of post-approval adverse drug experience information and fluoroquinolone class statements regarding retinal toxicity in cats. Notice of approval was published March 23, 2006.

CVM has published in the *Federal Register* notice of the approval of these Abbreviated NADAs (ANADA)

HEIFERMAX 500 (melengestrol acetate) Liquid Premix and RUMENSIN (monensin sodium) single-ingredient Type A medicated articles to make two-way combination drug Type C medicated feeds (ANADA 200-422), filed by Ivy Laboratories, Division of Ivy Animal Health, Inc. The ANADA provides for use of single-ingredient Type A medicated articles containing melengestrol and monensin to make two-way combination drug Type C medicated feeds for heifers fed in confinement for slaughter. Ivy Laboratories' ANADA 200-422 is approved as a generic copy of Pharmacia and Upjohn's NADA 125-476 for combination use of MGA 500 (melengestrol acetate) Liquid Premix and RUMENSIN in cattle feed. Notice of approval was published April 21, 2006.

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Approvals for March and April 2006 *(Continued)*

Abbreviated NADAs (Continued)

FLUNAZINE (flunixin meglumine) Injectable Solution (ANADA 200-387), filed by Cross Vetpharm Group Ltd. The ANADA provides for the veterinary prescription use of flunixin meglumine injectable solution for the alleviation of inflammation and pain associated with musculoskeletal disorders in the horse. It is also recommended for the alleviation of visceral pain associated with colic in the horse. In cattle it is indicated for the control of pyrexia associated with bovine respiratory disease and endotoxemia, and is also indicated for the control of inflammation in endotoxemia. Cross Vetpharm Group's Flunixin Injectable Solution is approved as a generic copy of Schering-Plough Animal Health's BANAMINE (flunixin) Solution, approved under NADA 101-479. Notice of approval was published March 31, 2006.

CVM has published in the *Federal Register* notice of the approval of these Supplemental ANADAs

TRI-OTIC (gentamicin sulfate, USP; betamethasone valerate, USP; and clotrimazole, USP) Ointment (ANADA 200-229), filed by Med-Pharmex, Inc., that provides for the treatment of acute and chronic canine otitis externa associated with yeast (*Malassezia pachydermatis*, formerly *Pityrosporum canis*) and/or bacteria susceptible to gentamicin. The supplemental ANADA provides for a new container size, a 15-g bottle. Notice of approval was published April 3, 2006.

Flunixin (flunixin meglumine) Injection (ANADA 200-308), filed by Norbrook Laboratories. The supplemental ANADA provides for the veterinary prescription use of flunixin meglumine solution by intravenous injection in lactating dairy cattle for control of fever associated with bovine respiratory disease and endotoxemia, and for control of inflammation in endotoxemia. Notice of approval was published March 29, 2006.

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