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Center for Veterinary Medicine
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CVM Involved in Counter-Terrorism Activities

Experts suspect that if animals were ever used as a target of terrorism, the attack at first might not look like terrorist activity, but instead resemble a case of feed contamination or a disease outbreak. Therefore, the Federal government has included the Food and Drug Administration's Center for Veterinary Medicine in its counter-terrorism initiative so the potential for attacks on food or animals can be addressed. Here is an update about FDA's activities in counter-terrorism.

FDA/CVM Responds to Homeland Security Directive

by Alfred Montgomery, D.V.M.
CVM Office of Counter-Terrorism Coordinator

The Food and Drug Administration is focused on protecting the safety of the food and feed supply, so when President Bush issued a Presidential Directive ordering the Federal government to develop protections against terrorism, FDA's Center for Veterinary Medicine (CVM) responded.

Due to the present climate of concern over terrorism, President Bush has established a new national policy that directs departments and agencies to protect the food and feed supply from a terrorist attack, major disasters, and other emergencies.

Dr. Alfred Montgomery, CVM Office of Counter-Terrorism Coordinator

Homeland Security Presidential Directive-9 ("Directive-9"), issued on January 30, 2004, calls for a cross-government effort to collect information on food, public health, water quality, and animal, plant, and wildlife diseases.

The Federal Food, Drug, and Cosmetic Act states that "the term 'food' means articles used for food or drink for man and other animals." So, when charged with protecting the food supply, FDA is also charged with protecting animal feed.

Although the leadership role under this directive falls to the Department of Homeland Security, many parts of the Federal government are involved in implementing the directive, including the Department of Health and Human Services, the U.S. Department of Agriculture (USDA), and the Environmental Protection Agency.

The goal of Directive-9 is to establish integrated surveillance systems to quickly detect emerging diseases, pests, toxic substances, and radioactive agents that threaten agriculture and the food supply. As a part of this directive, laboratory results and other information must be integrated from Federal, State, and local sources. This is a huge undertaking when one considers the number of the agencies within Federal, State, and local governments, some of which can be large. For instance, USDA's agencies include the Animal and Plant Health Inspection Service and the Food Safety and Inspection Service. Also included would be all State Veterinary Diagnostic Laboratories, FDA, and other Federal and State counterparts.

CVM's role under Directive-9 will be to incorporate into a database the information collected from surveillance of animal feeds. Presently, CVM oversees a program of sampling and analyzing animal feeds for contaminants, such as biological or chemical hazards, that pose a threat to public and animal health. FDA laboratories analyze feed for certain microbes, pesticides, drugs, and other chemicals known to have

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potential adverse affects on the health of animals or people.

Animal Feed Safety System

CVM will also incorporate its Animal Feed Safety System (AFSS) initiative, started last year to develop a new approach to feed safety, into its counter-terrorism work.

CVM began the AFSS initiative because of several feed contamination concerns that became apparent in the past few years, including for instance bovine spongiform encephalopathy, mycotoxins, PCBs, dioxins, and salmonella.

In addition, the AFSS is a way to address the fact that the U.S. has no unified, comprehensive set of feed safety standards that would cover the thousands of feed manufacturers and ingredient suppliers across the country.

The animal feed standards in use today emphasize end-product sampling.

By contrast, AFSS would consider a risk-based system that would detect hazards before feed products are distributed, thereby minimizing detrimental animal and human health effects from the hazards in the feed supply.

This sort of system would also work well under a counter-terrorism program, because AFSS would encourage detection of intentionally inserted hazards.

CVM sponsored a workshop on AFSS last September. Participants included representatives of the feed industry, the livestock production industry, and State feed control officials.

CVM staff is currently reviewing the comments from the meeting, which will be used to develop the AFSS program. (The transcript and other information from the meeting have been posted on CVM's Website at *www.fda.gov/cvm*. Search under "AFSS.")

Presidential Directive-9

The White House developed Homeland Security Presidential Directive-9 to call on the Federal government to establish a national policy to protect U.S. food and agriculture by becoming aware of the threats and mitigating them.

The food production system in the U.S. is an "extensive, open, interconnected, diverse, and complex structure providing potential targets for terrorist attacks," according to the directive. "We should provide the best protection possible against a successful attack on the U.S. agriculture and food system, which could have catastrophic health and economic effects," it says.

Here is a description of the directive.

- Directive-9 directs the agencies to prioritize sector-critical infrastructure to establish protection needs, and develop awareness and early capabilities to recognize threats to agriculture and the food supply. It also directs agencies to mitigate vulnerabilities at critical production points and to enhance response and recovery procedures.
- The directive establishes the Secretary of Homeland Security as coordinator of the overall national efforts to implement the efforts of the involved government agencies and private sectors to protect critical infrastructure and key resources.
- To provide an early warning system, Directive-9 requires affected Federal agencies to "develop robust, comprehensive, and fully coordinated surveillance and monitoring systems—including international information—for animal disease, plant disease, wildlife disease, food, public health, and water quality that provides early detection and awareness of disease, pest, or poisonous agents."
- As a part of this surveillance and detection system, agencies must develop nationwide laboratory networks for food, animal health, plant health, and water quality that integrate existing resources. FDA's electronic data communication system called eLexnet will be instrumental in achieving the goal of unifying these different methods of surveillance to increase our awareness capacity. eLexnet stands for "Electronic Laboratory Exchange Network." It is meant to be a "seamless" web-based information network designed to permit health officials at multiple government agencies to compare and coordinate laboratory analysis findings. Laboratories of FDA, the U.S. Department of Agriculture's Food Safety and Inspection Service, and the Department of Defense are actively entering data into this system. Also 18 State agriculture and 29 State health agencies are submitting data.
- Directive-9 requires the Departments of Agriculture, Health and Human Services, and Homeland Security to continue the update of vulnerability assessments of agriculture and the food sectors every two years. With the development of AFSS, CVM has begun a vulnerability assessment of the animal feed industry. CVM has also assisted the Animal and Plant Health Inspection Service in developing its assessment. These assessments will be ongoing. Moreover, Federal agencies will build on existing efforts and expand common inspection methods for agriculture and feed items entering the U.S.
- The directive requires Agencies to develop a National Veterinary Stockpile of therapeutic products that can be deployed within 24 hours of an outbreak.

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FDA VETERINARIAN

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CVM'S INVOLVEMENT IN COUNTER-TERRORISM ACTIVITIES

Database for Rapid Response to Feed Contamination

As part of the counter-terrorism initiative, the Center for Veterinary Medicine is overseeing a contract with Iowa State University to establish a national database linking participating State-run animal diagnostic laboratories that can be quickly called on when a feed contamination case is discovered.

The U.S. has at least 64 State veterinary diagnostic labs across the country—with at least one lab in nearly every State—and all are possible resources in a feed contamination event, whether the contamination occurred naturally or by terrorist activity. But until recently the labs were not linked. No one had a sure way to find out quickly which lab could do the needed analysis when a feed problem became evident.

Now, under a grant from the Food and Drug Administration, Iowa State University has developed a database of State labs. The database was created for counter-terrorism.

According to Dr. Gary Osweiler, Director, Veterinary Diagnostic Laboratory, Iowa State University, and director of the database project, the database is simply "a directory" of State vet diagnostic labs, and it contains the address of the labs, key individuals to contact at them, and a description of the tests the labs do.

State labs are not all the same, Dr. Osweiler said. They may perform a range of both screening tests and more complete or quantitative tests. Also, different laboratories accept different combinations of samples, for instance environmental samples or animal tissues.

The lack of uniformity among labs makes a database that identifies the attributes of each especially important when a large number of livestock are affected by an unknown toxin, and successful treatment will depend on how quickly the exact cause of the problem can be determined, he said.

By using the database, investigators can get a head start on discovering the cause of the problem. They will be able to consult the database to select the most appropriate lab to analyze samples. It may be the local lab, or one a few States away, Dr. Osweiler said. And, by using the database, the investigator will have the information needed to get in touch with the lab.

Currently, the Iowa State team is developing a computer interface that will permit easy use of the database. The project is scheduled to be completed during the current fiscal year, which ends September 30, 2004.

The database is not complete, Dr. Osweiler said. "It's a good start. It will help us identify the capabilities of State labs," he said, adding, "We are looking for a higher state of readiness" by adding more information about the depth of abilities the labs have.

FDA/CVM Responds to Homeland Security Directive *(Continued)*

- Directive-9 mandates support for higher educational programs about the protection of animal, plant, and public health. The directive also asks for research and development in this area as well as the establishment of university-based "Centers of Excellence" in agriculture and food security.

It is clear that the directive calls on FDA and CVM to coordinate effectively with other Federal agencies to protect the food and agriculture in America. The key modes of implementation as expressed in various aspects of Directive-9 are to expand already existing systems, enhance cooperative efforts already in place, and identify and bolster those areas that need reinforcement.

CVM Issues Guidance on the Unapproved Use of Hormone Implants in Veal Calves

On April 2, the Center for Veterinary Medicine announced that it was implementing special public safety measures in response to recent evidence of illegal use of growth-promoting hormone implants in veal calves.

Growth-promoting hormones are approved for use in ruminating cattle, but they have never been approved for use in non-ruminating veal calves. CVM believes there are differences between the way ruminating and non-ruminating cattle process and eliminate such hormones.

On April 2, CVM issued a guidance that describes the four conditions veal producers must meet to be able to sell implanted calves for veal:

1. The veal calf cannot be slaughtered for at least 63 days after it was implanted.
2. The veal calf must be presented for slaughter before June 6, 2004.
3. The livestock producer must have implanted the veal calf "in accordance with labeled dose for beef, in accordance with the directions on the implant, and in the proper location," which is under the skin of the ear.
4. The producer also must present appropriate certification outlined by a notice issued by the Food Safety and Inspection Service of the U.S. Department of Agriculture (USDA).

During an April 2 teleconference with reporters, CVM Director Dr. Stephen Sundlof explained, "We researched all the information we have and came up

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Public Health Section at AVMA Convention to Focus on Bacterial Pathogens in Animal Feed

by Joseph Paige, D.V.M.

The Center for Veterinary Medicine (CVM), with generous support from the American College of Veterinary Preventive Medicine and the American Association of Food Hygiene Veterinarians, will be chairing a Food Safety Section entitled "The Public Health Significance of Pathogens in Animal Feeds" during this year's American Veterinary Medical Association (AVMA) Annual Convention.

The 141st AVMA Convention will be held at the Pennsylvania Convention Center Philadelphia, Pa., July 24-28, 2004. The section on Food Safety is scheduled for Tuesday, July 27, beginning at 8:15 a.m., and ending at noon.

The Food Safety Section will address the significance of bacterial pathogens in animal feeds. We anticipate that it will continue the dialogue and collaboration initiated during a Centers for Disease Control and Prevention's (CDC) Public Health workshop, held in January of this year on "Bacterial Contamination of Animal Feeds and the Human Health Consequences," and the Food and Drug Administration/CVM public meeting to discuss the potential development of a comprehensive, risk-based Animal Feed Safety System held in September last year.

In order to address the issue of the significance of bacterial pathogens in animal feeds, the organizers of the Food Safety Section have assembled an internationally renown cadre of speakers representing public health, academia, regulatory science, policy making, and the feed industry.

The Center encourages those in the agriculture and veterinary community at large to attend this Food Safety Section.

The agenda follows in the table below.

2004 AVMA Food Safety Section

THE PUBLIC HEALTH SIGNIFICANCE OF PATHOGENS IN ANIMAL FEEDS

Moderator: Dr. Joseph Paige, Division of Compliance*, FDA/CVM

Focus: ***To present an overview of pathogens isolated from animal feed commodities***

8:15 a.m.	**A Discussion of the FDA/CVM Animal Feed Program** ***Dr. George Graber***, Deputy Director, Office of Surveillance and Compliance*, FDA/CVM
8:40 a.m.	**Systematic Monitoring of Feeds and Ingredients for Microbial, Chemical, and other Hazards that Pose a Food Safety Risk** ***Dr. John Kaneene***, Mich. State Univ., Chairman, Population Medicine Dept.
9:05 a.m.	**The Isolation of *Salmonella enterica* and *Escherichia coli* 0157:H7 from Animal Feed** ***Dr. Tom Blasser***, Wash. State Univ., College of Veterinary Medicine
9:30 a.m.	**BREAK**
10:00 a.m.	**National Antimicrobial Resistance Monitoring System (NARMS): The Linkage of Animal Feed Survey Data with NARMS** ***Dr. Marcia Headrick***, FDA/CVM NARMS Coordinator
10:25 a.m.	**Animal Feed as a Source of Human Foodborne Illness** ***Dr. Fred Angulo***, Chief, Foodborne and Diarrheal Diseases Branch, CDC
10:50 a.m.	**The Industry Perspective: The Use of Animal Proteins in Feed Rations: Are There Animal and Human Health Implications?** ***Dr. Don A. Franco***, Diplomate ACVMP, and industry consultant
11:15 a.m.	**PANEL DISCUSSION** **Questions and Answers** **Moderator: *Dr. Linda Tollefson***, Deputy Director, CVM

(* indicates change in title from earlier announcements)

CVM Issues Guidance . . . *(Continued)*

with a very conservative estimate of the time it would take for any residues of these drugs to fall below any concentration that we would consider to be of public health concern. That very conservative estimate is 63 days."

CVM's analysis was based on the best information available at the time and on the conditions outlined in the guidance, including that this is a one-time event and that illegal implants will not continue to occur.

The problem came to light earlier this year when USDA inspectors found indications of hormone treatment in veal calves brought to slaughter. The growth-promoting hormones were implanted as small pellets in the ear of the calf. The hormones involved may include progesterone, testosterone, estradiol, zeranol, and trenbolone.

Information about the requirements and a copy of the guidance document are available on CVM's website. (Search under "Guidances" for Guidance for Industry #172.)

CVM Takes Initial Steps to Implement Animal Drug User Fees Under ADUFA

As one of its first steps to implement the Animal Drug User Fee Act (ADUFA), the Center for Veterinary Medicine (CVM) in March published a guidance document explaining user fees and waivers.

The goal of ADUFA is to provide additional resources to the Food and Drug Administration so that CVM can improve its ability to promptly review drug applications.

Congress passed ADUFA in November 2003 and passed the budget appropriation in January of this year to enable the Center to start the process of implementing ADUFA.

Under ADUFA, FDA can collect a total of $5 million in fiscal year 2004, $8 million in fiscal year 2005, and $10 million in the next three fiscal years (through fiscal year 2008), for a total for all five years of $43 million.

FDA can collect four types of fees from drug sponsors; three of them on an annual basis and one that's linked to applications. The annual fees are for animal drug products, establishments that produce animal drugs, and drug sponsors that submit animal drug applications or investigational animal drug submissions. Application fees are collected for animal drug applications or supplements submitted after September 1, 2003.

FDA performance goals

In exchange for user fees, FDA and CVM promised an improved level of performance that could not be achieved without the additional revenue.

FDA committed to the goals, which will be phased in over the next five years, in a letter to Congress, presented to lawmakers while the user fee legislation was pending.

CVM has committed, by September 30, 2008, to:

- Review and act on 90% of all completed new animal drug applications within 180 days of submission. The interim goal during fiscal year 2004 is review times of no more than 295 days.
- Review 90% of non-manufacturing supplemental animal drug applications (applications that do not require safety or effectiveness data) within 180 days. The interim goal, for fiscal year 2004, is to reduce review times to 320 days.
- Review 90% of manufacturing supplements within 120 days.

The goal of ADUFA is to provide additional resources to the Food and Drug Administration so that CVM can improve its ability to promptly review drug applications.

- Review 90% of investigational animal drug study submissions within 180 days.
- Review 90% of the investigational protocols that are essential for making a decision on whether to approve the application or supplement within 50 days.
- Review 90% of administrative animal drug applications—applications submitted after all scientific decisions have been made during the investigational process—within 60 days.

In addition, FDA also has promised that CVM would review all applications that were pending before user fees were started within 24 months.

The measure will give manufacturers of animal health products not only shorter, but also more predictable review times, allowing them to better plan their business. FDA anticipates that the industry will see substantial savings as a result of the user fee act.

According to CVM Director Dr. Sundlof, the benefits of the user fees will not be limited to the drug industry or the Center, but will extend to the general public. "CVM and FDA will be able to provide greater public health protection by making as many safe and effective animal health products as possible available to food-animal producers and pet owners. With more approved products available, the need to use drugs in an extralabel fashion will be reduced."

The guidance FDA published in the *Federal Register* in March, titled "Animal Drug User Fees and Fee Waivers and Reductions," is the first guidance published under ADUFA. It describes the fees drug sponsors must pay and the potential fee reduction and waivers the industry can request.

Fee rates

The first fee amounts, which FDA published in February, are for application fees. In fiscal year 2004, the fee for animal drug applications is $61,000; for supplements it is $30,500. That rate was determined based on the expected number of applications for the year.

In April FDA announced the rates for product, establishment, and sponsor fees.

For fiscal year 2004, the product fee rate is $1,750, the establishment fee rate is $23,950, and the sponsor fee rate is $15,450.

FDA was scheduled to issue invoices for the fees on or about May 1, 2004. Those invoices will be due and payable within 30 days. Complete payment instructions will be included with each invoice. FDA will issue additional invoices after October 1, 2004, for any products, establishments, and sponsors that become subject to these fees after

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CVM Takes Initial Steps to Implement Animal Drug User Fees *(Continued)*

April 1, 2004, and these invoices will likewise include complete payment instructions.

ADUFA established the total amount FDA can collect under each of the fees. For fiscal year 2004, the total that can be collected under each type of fee is $1,250,000, totaling $5 million for all four fees. CVM decided on the rates by calculating how much revenue FDA would have to collect for each product and from each establishment and sponsor to reach the total of $1,250,000 in each category.

For example, CVM estimated that FDA can collect user fees for 714 products. Therefore, it will have to collect $1,750 for each product to reach the total of $1,250,000.

CVM also calculated that FDA will collect fees of $23,950 from each of the estimated 52 establishments and fees of $15,450 from each of the estimated 81 sponsors.

To arrive at its final estimates of products, establishments, and sponsors, CVM adjusted the expected totals to compensate for expected fee waivers and reductions. Descriptions of the waivers and reductions were given in Guidance for Industry #170, which published on March 15.

Waivers

ADUFA specifies five situations in which FDA could reduce or waive user fees, and the guidance published in March explains how FDA is interpreting the law as it pertains to waivers.

The guidance also gives an explanation of the procedures for requesting fee waivers or reductions, and a description of the supporting information the sponsor will be required to supply.

FDA can grant a waiver or reduction if the fees would pose a barrier to innovation, exceed FDA's present and future costs, are for supplemental applications providing for free-choice Type B and C medicated feeds, or are for drugs used solely in minor species or for minor uses. Also the fees can be waived or reduced on the first application submitted by a small business.

For more information, refer to the guidance document available on CVM's website. Click on "ADUFA."

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Comings and Goings

NEW HIRES

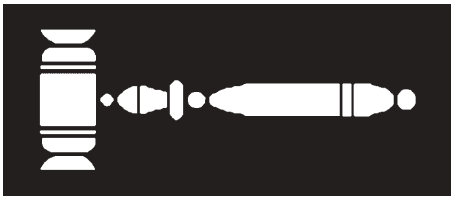
- Todd Blessinger, Ph.D., Mathematical Statistician, Office of New Animal Drug Evaluation
- Oscar A. Chiesa, Ph.D., Visiting Scientist, Office of Research
- Charles P. O'Brien, Chemist, Office of New Animal Drug Evaluation

CORRECTION

The previous edition of *FDA Veterinarian* incorrectly reported that Francisca Stone had retired. She has not retired and continues to work for CVM's Office of Surveillance and Compliance.

Regulatory Activities

by Marilyn Broderick
CVM Communications Staff



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

- John A. White, Owner, Joharra Dairy Farms, Casa Grade, AZ
- Donna Williams, Owner/President, H.B. Williams, Inc., Kingsley, PA
- Jason E. Nunes, Co-Owner, Nunes Family Dairy, LLC, Buhl, ID
- Larry B. Peterson and Marlene Peterson, Owners, Larry Peterson Dairy, Hilmar, CA

The above violations involved sulfadimethoxine in a dairy cow, neomycin in a bob veal calf, sulfamethazine in a dairy cow, and tetracycline in a dairy cow.

A warning letter was sent to Attica Veterinary Associates, P.C., Attica, NY, because an investigation revealed serious deviations from Extralabel Drug Use in Animals. The extralabel use of approved animal drugs by veterinarians is allowed provided that such use or intended use is by or on the lawful order of a licensed veterinarian within the context of a veterinarian-client-patient relationship and in compliance with extralabel use regulations found in 21 CFR Part 530. The veterinary practice sold veterinary prescription drugs not approved for the use in lactating dairy cows without benefit of a lawful prescription and outside the bounds of a valid veterinarian-client-patient relationship. These actions caused the veterinary prescription drugs to be adulterated within the meaning of Section

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Changes in CVM's Office of Surveillance and Compliance

The Center for Veterinary Medicine has named Dr. Daniel G. McChesney to the position of Director, Office of Surveillance and Compliance (OS&C), and Dr. George Graber to the position of Deputy Director OS&C.

Dr. McChesney became OS&C Director on October 19, 2003.

He has been with CVM since 1990. His first position was a microbiologist in CVM's Division of Animal Feeds, where he served as the Center's expert on microbial contaminants of animal feed, specializing in salmonella control and the application of Hazard Analysis and Critical Control Point programs to the feed industry. He served as the acting director of the Division of Compliance in OS&C from May to September 1996. Just prior to accepting the position of OS&C Director, Dr. McChesney was the deputy OS&C director.

Dr. McChesney received a B.S. degree in biology from Mercer University in Macon, GA, and his M.S. and Ph.D. degrees in cell and molecular biology from the Medical College of Georgia, Augusta. Upon completing his degree, he entered the U.S. Army and was stationed at the Walter Reed Army Institute of Research (1978-1987), where he served as a research microbiologist. After completing his active military service, he was a senior investigator at the Armed Forces Radiobiology Research Institute and was responsible for determining the mechanism involved in increasing survival after radiation injury.

Dr. Daniel McChesney, Director, Office of Surveillance and Compliance

Dr. George Graber, Deputy Director, Office of Surveillance and Compliance

"Dr. McChesney is well known and respected within CVM and the Food and Drug Administration, as well as by CVM's external stakeholders. His experience with CVM programs has demonstrated his strong ability to carry out the Center's mission," according to Center Director Dr. Stephen F. Sundlof

Dr. Graber was named Deputy Director for the OS&C on March 8, 2004. Dr. Graber has been with FDA for 33 years and served as the Director of the Division of Animal Feeds for 25 years.

He received his B.S. and M.S. degrees in animal science from Rutgers University and his Ph.D. from the University of Illinois.

In naming Dr. Graber to his new role, Dr. McChesney said, "Dr. Graber has provided valuable scientific and policy leadership to the Office on several very important issues, such as bovine spongiform encephalopathy, chronic wasting disease, dioxin, the Animal Feed Safety System, and the medicated feed program, which makes him highly qualified to serve in this broader role in the Center."

Regulatory Activities *(Continued)*

501(a)(5) and misbranded within the meaning of Section 501(f)(1) of the Act.

Warning letters were sent to the following individuals and firms for offering animals for slaughter that contained illegal residues and for deviations from the regulations for Extralabel Drug Use by using animal drugs in a manner contrary to their approved labeling or conditions of use:

- Robert D. Hogg, Owner, Sun Valley Jerseys, Ontario, CA
- Brian C. Blevins, Owner, Dairyland Milk Company, Stanfield, AZ
- Robert J. Schell, D.V.M., Co-Owner, Schell's Pine Grove Dairy, Altura, MN
- Walter Bones, President, Turner County Dairy, LLP, Parker, SD
- Jody J. Neal, Co-Owner, Orleans Poverty Hill Farm, Albion, NY
- Joseph R. Hemauer, Owner, Kettle Edge Dairy, Plymouth, WI
- Carlton C. Bull, Owner, Cha-Liz Farm, LLC, West Chazy, NY
- James B. Cnossen, Co-Owner, Cnossen Dairy, Jerome, ID

The above violations involved penicillin in dairy cows, oxytetracycline in a dairy cow, flunixin in a dairy cow, sulfadimethoxine in dairy cows, and sulfamethazine in a dairy cow.

Adverse Drug Experience Reports Lead to Label Changes, Other Actions for Safer Animal Drugs

More than 2,000 reports on adverse experiences from drugs reach the Center for Veterinary Medicine each month. Analyzing the information is a substantial task, but the result is safer animal drugs.

About 99% of all the Adverse Drug Experience (ADE) reports the Center receives come from animal drug manufacturers, who are required to pass along to CVM such reports received from veterinarians and others who use the products.

As information is received, CVM's staff continually works to sort it all out.

Animal drug regulations require drug manufacturers to report any serious adverse reaction within 15 days of the event. More routine adverse events are reported at scheduled times—semiannually during a drug's first two years on the market following approval, then annually after that.

When the reports reach CVM, the staff evaluates the adverse events for seriousness and frequency. The staff uses a variation of a system used to evaluate adverse experience reports about human drugs.

The reviewer uses a scoring system to determine the likelihood that the drug was positively linked, probably linked, or possibly linked to the adverse event. The reviewer also notes when the information available was not enough to draw a conclusion, and if the drug was used for an indication not on the label.

When the review indicates a slight to a strong link between the adverse event and the drug, information from the ADE is entered into a database that is available on CVM's website for public review. The database is updated monthly.

About 99% of all the Adverse Drug Experience (ADE) reports the Center receives come from animal drug manufacturers, who are required to pass along to CVM such reports received from veterinarians and others who use the products.

Triggers

CVM is likely to ask the drug sponsor to make labeling changes or take other steps, such as sending a "Dear Doctor" letter to its client-veterinarians, if certain trigger points appear in the database. (To see "Dear Doctor" letters, go to CVM's website and search using that term.)

For instance, if certain adverse experience signs show up frequently in the database, and the causality scores are in the possible-to-probable range, CVM officials are likely to contact the drug sponsor about label changes or other steps.

Also, if the scores are in the definite range and the adverse experience is severe, such as death, CVM officials are likely to ask the manufacturer to take some steps, even though the adverse events are not frequent.

Sometimes the ADE finding leads the company to revise the label—for instance to add safety warnings or to highlight information already there. And often the company will send out the "Dear Doctor" letter highlighting the change for veterinarians.

NSAIDs

The Center's recent work to revise labels on some relatively new pain relief drugs for dogs demonstrates how the ADE process works.

In the past few years, CVM has approved several non-steroidal anti-inflammatory drugs (NSAID) for use in dogs. NSAIDs are not new. They have been available for human use for several years, and examples include many over-the-counter products such as aspirin, acetaminophen, ibuprofen, and naproxen.

NSAIDs are effective in canines for the relief of pain associated with osteoarthritis or for treating postoperative pain. Some older NSAID products FDA approved for use in animals include etodolac, carprofen, and deracoxib. Newer ones include meloxicam and tepoxalin approved for use in dogs.

Recently approved NSAIDS typically are what scientists call cox-selective agents. The drugs are believed to be safer than earlier NSAIDs, but they are not completely safe.

Information in CVM's ADE database indicates that the most common adverse experiences that have been reported following the use of an NSAID in a dog are vomiting, anorexia, depression, and diarrhea. Less commonly reported but more serious ADEs include gastric ulceration, intestinal ulceration, renal failure, hepatic failure, and even death.

The ADE reports on NSAIDs have led to revised labels. For instance, CVM has required manufacturers to add a label section that specifically addresses these "post-approval experiences."

(Continued, next page)

Adverse Drug Experience Reports . . . *(Continued)*

Beyond Label Changes

Beyond official requests for label changes, CVM staff can use the ADE reports in other, non-regulatory ways to make veterinary medicine safer for animals. NSAIDs provide a good example of how that works, too.

The analysis of the ADEs for NSAIDs led CVM to recommend that veterinarians:

- Pay attention to dosage, and dose strictly according to the patient's body weight. Some NSAID products have two dose levels, one for long-term use for osteoarthritis patients, and another higher dose for short-term post-operative pain. Even better than dosing based strictly according to body weight, veterinarians can determine the dose for each dog individually by titrating the dose to desired effect.
- Screen their patients for renal and hepatic disease and monitor patients during treatment. NSAIDs can be nephrotoxic and hepatotoxic.
- Optimize surgical patients' hydration status by providing parenteral fluids. Dehydrated patients should not receive NSAIDs.
- Allow adequate time for their patients to "wash-out," or eliminate from their systems, previous NSAID or corticosteroid treatments before a new NSAID treatment is administered. The length of time that constitutes "adequate" has yet to be firmly determined, but product manufacturers can help veterinarians determine current recommendations.
- Read the NSAIDs label and understand the risks presented by the use of the NSAID products. Veterinarians should also make it a point to communicate the risk information to the pet owners. Risk information is often available on the client information sheets that come with the NSAID product. The veterinarian should be sure that the client receives any information sheet that accompanies the product.

Consumer Concerns

Not all the information CVM reviews comes from the formal ADE reporting system. Some information comes directly from consumers.

Although the total number of ADEs from consumers probably equals less than 1% of all the reports the Center receives, the reports from consumers often provide valuable information about how veterinarians are keeping their clients informed.

The consumer information typically comes to CVM via the adverse event telephone "hotline." CVM originally established the hotline for use by veterinarians, but the majority of calls come from consumers who found the phone number on CVM's website.

CVM officials recently conducted an analysis of the past two years of calls to the hotline, and the review indicated clearly that consumers often will become heavily involved with the treatment their pets have been getting and that they use the Internet to find out more about the drugs their pets get.

In addition, the analysis showed that consumers are willing to tell CVM if they believe they did not get all the information they should have from their veterinarians about the drugs prescribed for their pets.

Victoria Hampshire, V.M.D., the adverse drug events coordinator in CVM's Office of Surveillance and Compliance, recently wrote in an article for the *Journal of American Veterinary Medicine Association* about the analysis.

Dr. Hampshire said that pet owners are calling the hotline to report that their veterinarians did not provide the label information and client information sheets that the owners later found on CVM's website.

According to Dr. Hampshire, CVM considers the drug label as the first source of information for veterinarians about the drug. The label is the result of extensive, science-based, regulatory review. The label describes safety and efficacy factors about the drug, and it describes the animals for which its use is intended.

Besides presenting information on the label, manufacturers also can use a client information sheet, which is information that animal owners should have beyond what is on the label. Sometimes the manufacturer decides that a client information sheet is needed, and sometimes CVM decides one is needed and requests the manufacturer to develop it. The client information sheet can be as important as the drug's label to ensure the safe and proper use of the drug.

In the article, Dr. Hampshire also advised veterinarians to:

- Give their customers any client information sheets that come with the drug.
- Read the labels to identify contraindications, safety information, and warnings about what animals would not be good candidates for medication.
- Make sure that labels have not changed. A large stock of a drug could mean a long time between reorders. The label could change during that time, but the veterinarian would not be aware of the change.

(Much of the information generated for this article was provided by Thomas J. Moskal, D.V.M., Veterinary Medical Officer with the Division of Surveillance.)

BSE INSPECTION UPDATE

CVM Reports Latest BSE Inspection Figures

As of April 17, the Food and Drug Administration had received more than 29,000 reports of inspections done under the ruminant feed rule designed to prevent the establishment or spread of bovine spongiform encephalopathy (BSE) in the U.S.

About 70% of the BSE feed rule inspections have been done by States, and the rest by FDA personnel. Completed inspection reports are regularly added to the BSE inspection database available through the Center for Veterinary Medicine's website.

The inspection results are recorded in one of three classifications:

- An **OAI (Official Action Indicated)** inspection classification occurs when significant objectionable conditions or practices were found and regulatory sanctions are warranted in order to address the establishment's lack of compliance with the regulation.
- A **VAI (Voluntary Action Indicated)** inspection classification occurs when objectionable conditions or practices were found that do not meet the threshold of regulatory significance, but do warrant advisory actions to inform the establishment of findings that should be voluntarily corrected. VAI violations are typically technical violations of the BSE feed rule, such as minor recordkeeping lapses and conditions involving non-ruminant feeds.
- Firms not classified as OAI or VAI are classified as **No Action Indicated**. This inspection classification occurs when no objectionable conditions or practices were found during the inspection or the significance of the documented objectionable conditions found does not justify further actions.

The classifications in the database are based on most recent inspectional finding. These findings were as of April 17.

The results presented here are reported here both by "segment of industry" and "in total." Because a single firm can be classified in more than one industry segment, the totals for the industry segments and the overall total may not be the same.

Renderers

These firms are the first to handle and process (i.e., render) animal proteins and to send these processed materials 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** – 238
- **Number of active firms handling materials prohibited from use in ruminant feed** – 159 (67% of those active firms inspected)
- **Of the 159 active firms handling prohibited materials,**
  - 0 firms (0%) were classified as OAI
  - 2 firms (1.3%) were classified as VAI

Licensed Feed Mills

FDA licenses these feed mills to produce medicated feed products. The license is required to manufacture and distribute feed using certain potent drug products, usually those requiring some pre-slaughter withdrawal time. This licensing has nothing to do with handling materials prohibited for use in feed for cattle and other ruminants under the BSE feed ban regulation. A medicated feed license from FDA is not required to handle materials prohibited under the feed ban.

- **Number of active firms whose initial inspection has been reported to FDA** – 1,088
- **Number of active firms handling materials prohibited from use in ruminant feed** – 338 (31% of those active firms inspected)
- **Of the 338 active firms handling prohibited materials,**
  - 1 firm (0.3%) was classified as OAI
  - 7 firms (2.2%) were classified as VAI

Feed Mills Not Licensed By FDA

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

- **Number of active firms whose initial inspection has been reported to FDA** – 5,100
- **Number of active firms handling materials prohibited from use in ruminant feed** – 1,115 (22% of those active firms inspected)
- **Of the 1,115 active firms handling prohibited materials,**
  - 6 firms (0.5%) were classified as OAI
  - 36 firms (3.2%) were classified as VAI

Protein Blenders

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

- **Number of active firms whose initial inspection has been reported to FDA** – 267
- **Number of active firms handling materials prohibited from use in ruminant feed** – 67 (25% of those active firms inspected)
- **Of the 67 active firms handling prohibited materials,**
  - 1 firm (1.5%) was classified as OAI
  - 2 firms (3.0%) were classified as VAI

Renderers, Feed Mills, and 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 utilizing prohibited materials. It does not include firms that only handle feed or feed ingredients that contain prohibited material.

- **Number of active renderers, feed mills and protein blenders whose initial inspection has been reported to FDA** – 6,503

(Continued, next page)

CVM Reports Latest BSE Inspection Figures *(Continued)*

- **Number of active renderers, feed mills and protein blenders processing with prohibited materials** – 542 (8.3% of those active firms inspected)
- **Of the 542 of active renderers, feed mills and protein blenders processing with prohibited materials,**
  - 7 firms (1.3%) were classified as OAI
  - 19 firms (3.5%) 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** – 10,393
- **Number of active firms handling materials prohibited from use in ruminant feed** – 1,842 (18% of those active firms inspected)
- **Of the 1,842 active firms handling prohibited materials,**
  - 11 firms (0.6%) were classified as OAI
  - 68 firms (3.7%) were classified as VAI

Total

- **Number of active firms whose initial inspection has been reported to FDA** – 14,037
- **Number of active firms handling materials prohibited from use in ruminant feed** – 2,474 (18% of those active firms inspected)
- **Of the 2,474 active firms handling prohibited materials,**
  - 11 firms (0.4%) were classified as OAI
  - 80 firms (3.2%) were classified as VAI

Administrative Law Judge Issues Initial Ruling on CVM Antimicrobial Proposal

Food and Drug Administration Administrative Law Judge Daniel J. Davidson issued his initial decision on March 16 on the Center for Veterinary Medicine's (CVM) proposal to withdraw approval of the New Animal Drug Application (NADA) for enrofloxicin for poultry, and ordered that the approval be withdrawn, effective on the date the initial decision becomes final.

This initial decision will become the final decision of the Commissioner of the Food and Drug Administration in the absence of the timely filing of exceptions by any participant or the filing of a notice that the Commissioner intends to review the decision.

The brand name of enrofloxicin for poultry is Baytril 3.23%, and the product sponsor is Bayer Animal Health.

Bayer requested a hearing, which was held in front of Judge Davidson April 28, 2003, to May 7, 2003.

CVM proposed to withdraw approval of the NADA based on the Center's determinations that:

- The use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter*, a pathogen to humans, in poultry;

This initial decision will become the final decision of the Commissioner of the Food and Drug Administration in the absence of the timely filing of exceptions by any participant or the filing of a notice that the Commissioner intends to review the decision.

- This fluoroquinolone-resistant *Campylobacter* is transferred to humans and is a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans; and
- Fluoroquinolone-resistant *Campylobacter* infections are a hazard to human health.

CVM proposed to withdraw the approval on the grounds that new evidence shows the product has not been shown to be safe.

The product is indicated for the control of mortality in chickens associated with *E. coli* organisms and control of mortality in turkeys associated with *E. coli* and *Pasteurella multocida* organisms.

Enrofloxacin belongs to the class of antimicrobial drugs called fluoroquinolones. Fluoroquinolones also are approved for use in humans. Fluoroquinolones are used routinely by physicians for the treatment of foodborne disease. These diseases have a major public health consequence in the U.S.

You can read the judge's decision on *http://www.fda.gov/cvm/index/updates/baytrilup.htm*.

CDC Hosts NARMS Scientific Meeting

by Marcia L. Headrick, D.V.M., M.P.H., CVM NARMS Coordinator, and Elvira Hall-Robinson, D.V.M., M.P.H., NARMS Epidemiologist

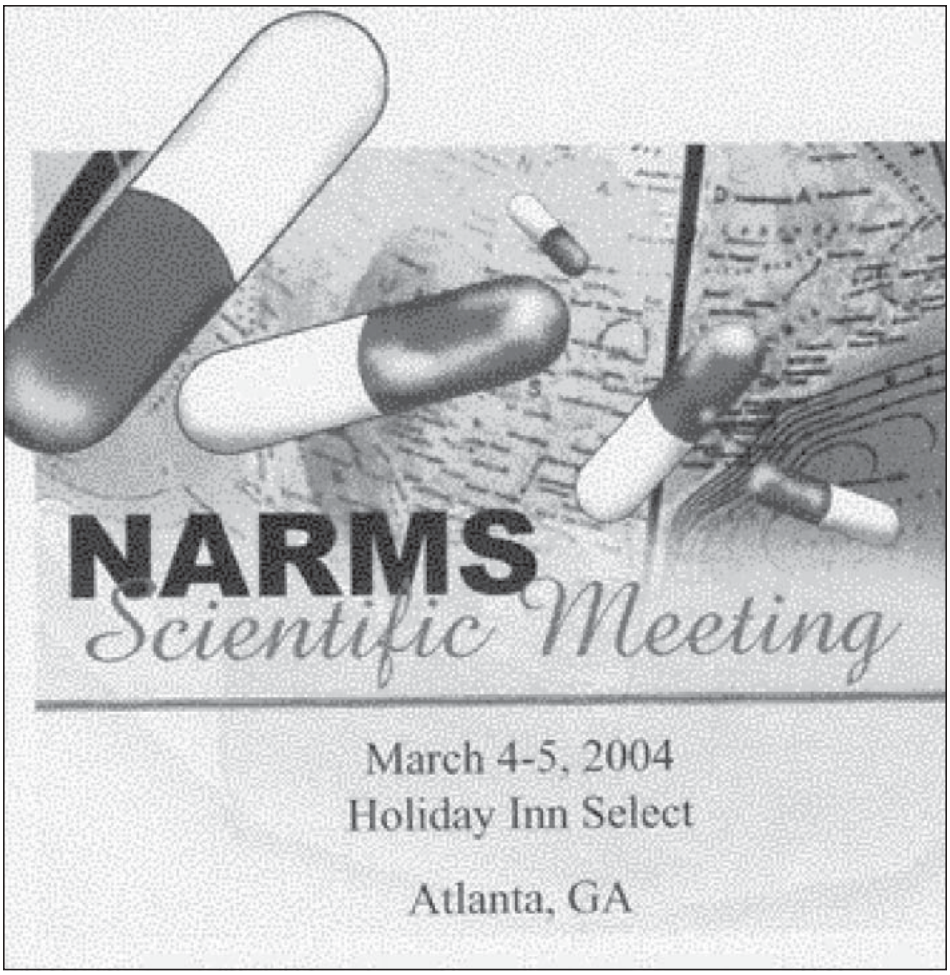
The Center's for Disease Control and Prevention (CDC), in collaboration with Food and Drug Administraion's Center for Veterinary Medicine (CVM) and the U.S. Department of Agriculture, sponsored a two-day meeting on the results from the National Antimicrobial Resistance Monitoring System – Enteric Bacteria (NARMS) and related antimicrobial resistance research.

The meeting was held March 4-5, 2004, in Atlanta, GA. The open scientific meeting was attended by more than 200 registrants including representatives from Federal and State government agencies, academia, industry, commodity groups, public interest groups, professional associations, and others interested in antimicrobial resistance research.

The meeting immediately followed the International Conference on Emerging Infectious Diseases, held in Atlanta, allowing participants to take advantage of two important back-to-back meetings that presented many common topics of interest.

The NARMS meeting included sessions on:

- NARMS Surveillance of Enteric Bacteria
- Clinical Consequences of Antimicrobial Resistance
- Recent Outbreaks of *S. Typhimurium* DT104
- Emerging Resistance among Clinically Important Antibiotics
- Multi-Drug Resistance
- Environmental Studies on Antimicrobial Resistance
- Antimicrobial Resistance in Commensal Bacteria
- Partner Perspectives on Antimicrobial Resistance
- International Perspectives on Antimicrobial Resistance
- NARMS Educational Activities



Representatives from Thailand, United Kingdom, Vietnam, India, Poland, Philippines, Denmark, and Canada made scientific presentations.

The agenda and presentations from the NARMS Scientific Meeting will be posted on the CDC NARMS website at *http://www.cdc.gov/narms/.*

The NARMS program plays an important role in the overall understanding of antimicrobial drug resistance. NARMS facilitates the determination of the prevalence of selected resistant enteric bacterial organisms in humans, animals, and retail meat; provides information on antimicrobial resistance to veterinarians and physicians; prolongs the lifespan of approved drugs by promoting the prudent and judicious use of antimicrobial drugs; and identifies areas for more detailed investigation.

NARMS also aids in antimicrobial resistance research by providing a national source of enteric bacterial isolates that is invaluable for research, such as diagnostic test development, discovering new genes and molecular mechanisms associated with resistance, for studying mobile gene elements, and for virulence and colonization studies.

For more information on the NARMS program, please contact Dr. Marcia Headrick, FDA CVM NARMS Coordinator, *mailto:mheadric@cvm.fda.gov* or call (706) 546-3689. Additional information on the NARMS program is also available on the CVM NARMS web page at *http://www.fda.gov/cvm/index/narms/narms_pg.html.*

CVM Releases Animal Feed Safety System Documents to Public

The Center for Veterinary Medicine on March 31 made information from last year's meeting about the Animal Feed Safety System (AFSS) available to the public, and provided documents that CVM drafted following the meeting.

The information is available in the Food and Drug Administration's Docket and can be accessed electronically (go to FDA's website, then to dockets, and then search for Docket #2003N-0312; or go to CVM's website and find the "UPDATE" on AFSS issued on March 31).

The Center intends that AFSS be a system that minimizes risks to animals consuming feed and to humans consuming food from animals.

Among the documents presented is one CVM staff drafted that defines the terms "comprehensive" and "risk based" as applied to AFSS. Another presents a draft outline of the "Elements of an animal feed safety system." Both documents are dated March 1, 2004.

The Center [CVM] intends that AFSS be a system that minimizes risks to animals consuming feed and to humans consuming food from animals.

In addition, the Docket has minutes of the AFSS meeting CVM sponsored in September 2003, copies of presentations made at that meeting, and reports from the meeting's breakout groups.

Comments concerning AFSS are welcome, and should be sent to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Comments should include Docket #2003N-0312. (Comments can also be sent electronically. See the March 31 "UPDATE" for more information.)

APPROVALS FOR JANUARY AND FEBRUARY 2004

New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
IDEXX Pharmaceuticals, Inc. (NADA 141-178)	Nitazoxanide Paste (Navigator)	Horses. For treatment of EPM caused by *Sarcocystis neurona*.	**ORAL**—The NADA provides for veterinary prescription use of a nitazoxanide oral paste for the treatment of equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*. *Federal Register* 01/06/04
Ridley Block Operations, Inc. (NADA 141-187)	Lasalocid (Bovatec 68) (Crystalyx Iono-Lyx)	Cattle. Increased rate of weight gain.	**MEDICATED FEED**—The NADA provides for use of Bovatec 68 (lasalocid) Type A medicated article to manufacture Crystalyx Iono-Lyx free-choice Type C medicated protein feed blocks containing 300 grams lasalocid per ton. The free-choice medicated feed protein block is used for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, and dairy and beef replacement heifers). *Federal Register* 01/09/04

Supplemental New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Merial Ltd. (NADA 140-841)	Ivermectin (Ivomec Pour-On for Cattle)	Cattle. Control infections and prevent re-infection with certain species of external and internal parasites.	**TOPICAL—**The supplemental NADA provides for topical use of 0.5% ivermectin solution on cattle to control infections and prevent re-infection with *Oesophagostomum radiatum* and *Dictyocaulus viviparus* for 28 days after treatment, *Cooperia punctata* and *Trichostrongylus axei* for 21 days after treatment, *C. surnabada* for 14 days after treatment, and *Damalinia bovis* for 56 days after treatment. In addition, the regulation is revised to remove two species of parasites, *Oesophagostomum venulosum* and *Chorioptes bovis*, which were codified in error during the original approval and the indication for *Cooperia spp*. is speciated as *Cooperia oncophora*, *C. punctata*, and *C. surnabada* to conform with current labeling practices. A veal calf warning statement is being added because residue depletion data for this class of cattle has not been submitted to the application. *Federal Register* 01/06/04
Pharmacia & Upjohn Co. (NADA 140-890)	Ceftiofur hydrochloride (Excenel RTU Sterile Suspension)	Cattle and Swine. For the treatment of bovine respiratory disease, acute bovine interdigital necrobacillosis, and acute metritis, and for the treatment/control of swine bacterial respiratory disease.	**INTRAMUSCULAR OR SUBCUTANEOUS**—The supplemental NADA provides updated susceptibility information for food-animal pathogens listed in the clinical microbiology section of labeling. *Federal Register* 01/16/04
Pharmacia & Upjohn Co. (NADA 140-338)	Ceftiofur sodium (Naxcel Sterile Powder for Injection)	Cattle, Swine, Sheep, Goat, Horse, Dog, Day-old Chicken, and Day-old Turkey Poult. For treatment of various bacterial diseases.	**INTRAMUSCULAR OR SUBCUTANEOUS**—The supplemental NADA provides updated susceptibility information for food-animal pathogens listed in the clinical microbiology section of labeling. *Federal Register* 02/11/04
Alpharma, Inc. (NADA 130-435)	Oxytetracycline hydrochloride (OxyMarine Soluble Powder)	Finfish fry and fingerlings. To mark skeletal tissues, most often the otoliths, of all finfish fry and fingerlings for subsequent identification.	**IMMERSION**—The supplemental NADA provides an added claim for the skeletal marking of finfish fry and fingerlings by immersion. The approval of this supplemental NADA relied on publicly available safety and effectiveness data contained in Public Master File (PMF) 5667, which were compiled under National Research Support Project 7 (NRSP-7), a national agricultural research program for obtaining clearances for use of new drugs in minor animal species and for special uses. *Federal Register* 02/11/04

(Continued, next page)

Supplemental New Animal Drug Approvals *(Continued)*

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Elanco Animal Health (NADA 095-735)	Monensin sodium (Rumensin 80)	Feedlot cattle. For prevention and control of coccidiosis in feedlot cattle.	**MEDICATED FEED**—The supplemental NADA provides for revised labeling for the use of single-ingredient monensin Type A medicated articles to make Type C medical feeds used for the prevention and control of coccidiosis in feedlot cattle. The regulations are being amended to remove a redundant entry for use of monensin in Type C medicated cattle feeds. *Federal Register* 02/11/04

Abbreviated New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Fort Dodge Animal Health, Division of Wyeth (ANADA 200-367)	Trenbolone acetate and Estradiol (Synovex T120, Synovex T80, Synovex T40)	Cattle. Increased rate of weight gain and improved feed efficiency.	**SUBCUTANEOUS IMPLANT**—The ANADA provides for the use of three different strengths trenbolone acetate and estradiol implants in cattle. Fort Dodge Animal Health's Synovex T120, Synovex T80 and Synovex T40 are generic copies of Intervet, Inc.'s Revalor-S, Revalor-IS, and Revalor-G, approved under NADA 140-987. *Federal Register* 01/06/04

Supplemental Abbreviated New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Ivy Laboratories, Division of Ivy Animal Health, Inc. (ANADA 200-346)	Trenbolone acetate and estradiol, and tylosin tartrate (Component TE-200 with Tylan)	Feedlot steers. Increased rate of weight gain and improved feed efficiency.	**SUBCUTANEOUS EAR IMPLANT**—The supplemental ANADA provides for the addition of a pellet containing 29 milligram tylosin tartrate to an approved subcutaneous implant containing trenbolone and estradiol used for increased rate of weight gain and improved feed efficiency. *Federal Register* 02/13/04

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