FDA VETERINARIAN
Center for Veterinary Medicine
July/August 2004 Vol. XIX, No. IV

New "MUMS" Legislation to Help Make Animal Drugs Available for Limited Uses, Minor Species

by Meg Oeller, DVM, and Jon Scheid, Editor

President Bush has signed legislation that will help make more medications legally available to veterinarians and animal owners to treat minor animal species and also uncommon diseases in the major animal species.

This legislation provides innovative ways to bring such products to market and helps pharmaceutical companies overcome the financial roadblock they face in providing limited-demand animal drugs, according to supporters.

Congress completed work on the measure July 20, and the President signed it on August 2. It was part of a legislative package that also included a food allergen labeling law.

The animal drugs measure is expected to benefit people who own small or unusual pets such as guinea pigs or ornamental fish, and it will likely be a great help to zoo veterinarians, supporters said. Before this, pharmaceutical companies could rarely afford to bring to market drugs for novel pets and zoo animals. The markets were just too small to generate an adequate financial return.

The standards for drug approval are those established by the Federal Food, Drug and Cosmetic Act, which is the legal authority the Food and Drug Administration (FDA) uses to approve animal drugs. Generating those data to meet these standards is an expensive process.

Animal drug companies can make more money by developing drugs that have broad uses, such as treating some of the 95 million cattle or 60 million hogs in the United States. The financial returns from these markets are much more likely to repay the costs of developing the drugs.

The goal of this legislation is to provide incentives to pharmaceutical companies to develop drugs for limited uses and to provide some alternative approaches to the usual drug approval process for limited-use animal drugs, thus changing the economic outlook for the drug approval process.

The new law, officially named "The Minor Use and Minor Species Animal Health Act of 2004," dubbed "MUMS" for Minor Use/Minor Species, provides some flexibility in getting limited-use drugs to market.

Minor use drugs are drugs for use in major species (cattle, horses, swine, chickens, turkeys, dogs and cats) that are needed for diseases that have a limited geographic range or affect a small number of animals. Minor species includes all animals other than the major species, which includes zoo animals, ornamental fish, parrots, ferrets and guinea pigs. Some animals of agricultural importance are also minor species. These include sheep, goats, catfish and honeybees.

The Center for Veterinary Medicine (CVM) was charged to develop policies, regulations or legislative options to facilitate drug availability for MUMS by a provision of "The Animal Drug Availability Act" of 1996.

After CVM published a report containing the initial concepts for MUMS, a coalition of animal drug sponsors and other affected parties began the process of talking to Congress about the legislation.

Key provisions

The new law will modify provisions of the Federal Food, Drug and Cosmetic Act in three ways.

- **Conditional Approval:** An expensive part of the drug approval process for companies is demonstrating that a drug is effective. Drug companies typically collect data from various clinical trials. Under MUMS, the sponsor of a veterinary drug can ask CVM for "conditional approval," which allows the sponsor to make the drug available before collecting all necessary effectiveness data, but

(Continued, next page)

In This Issue

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

What Does the MUMS Legislation Mean?

Congress has approved and the President has signed the Minor Use and Minor Species Animal Health Act. This legislation adds new options for approving limited-use drugs and provides for a new mechanism to legally market some unapproved products. Here is a discussion of what these changes will mean. Andrew Beaulieu, D.V.M., is CVM's Associate Director for Animal Health Policy and Operations, and Meg Oeller, D.V.M., a CVM specialist in the area of Minor Use and Minor Species (MUMS).

by Jon Scheid, Editor, based on a conversation with Dr. Beaulieu and Dr. Oeller.

What defines a minor species?

Over the years, the Center for Veterinary Medicane (CVM) and the animal health industry have followed the definition of minor species in the *Code of Federal Regulations*. This defines minor species by exclusion, meaning that the major species have been identified, and all others are considered minor species. Major species are cattle, swine, chickens, turkeys, horses, dogs and cats.

Historically, a species was considered to be a major species if it had a large enough population to generate a significant market for animal health products. This new law adds the definitions of major and minor species as well as the definition of minor use to the statute.

Under the new law, the Secretary of Health and Human Services has the authority to write a regulation to change a species classification from minor to major, but not from major to minor.

(Continued, next page)

New "MUMS" Legislation . . . *(Continued)*

after proving the drug is safe. The drug sponsor can keep the product on the market for up to five years, through annual renewals, while collecting the required effectiveness data. The revenue the product generates during this period will help the company defray the cost of collecting the data. After the sponsor has completed the effectiveness component, the sponsor can present that component to CVM for full approval of the product.

Under MUMS, FDA may refuse to renew the conditional approval if the company is not making sufficient progress toward collecting the effectiveness data.

- **Indexing:** In some cases, the potential market for a minor species drug is just too small to ever support the costs of the drug approval process, even under a conditional approval. The population may not be suitable for use in clinical studies because the animals are rare or valuable. In such cases, FDA now may add the drug to an index of legally marketed unapproved new animal drugs.

  After FDA determines that a drug could be eligible for listing on the index, the drug sponsor will use outside experts to review all of a drug's available safety and effectiveness information. The panel will provide a report to FDA/CVM of its findings so that the Agency may determine whether the drug should be placed on the index list.

  This provision will be especially helpful to veterinarians treating zoo or endangered animals or classes of animals that include several different species, such as ornamental fish.

  This provision will not be used for food animals with the exception of some early life stage uses, such as fish eggs. This provision would apply only to drugs for minor species, and not to minor uses of drugs in major species.

- **Designation:** This aspect of the legislation is similar to the "Orphan Drug Act" for humans, which helps pharmaceutical firms develop drugs for limited human uses. It provides incentives for approval. Grants to support safety and effectiveness testing will be available. Companies who gain approval for designated new animal drugs will be granted seven years of marketing exclusivity, which means the sponsor will face no competition in the marketplace for that use of the drug for that time.

Other provisions

The new law authorizes CVM to establish an office of Minor Use and Minor Species Animal Drug Development, which will be responsible for designating minor use and minor species animal drugs, administering grants, reviewing minor species drug index listing requests and serving as liaison to all parties involved with minor use or minor species drug development.

FDA VETERINARIAN

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs

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

Jon Scheid, Editor

Joanne Kla, Assistant Editor

Published bi-monthly.

Articles are free of copyright and may be reprinted.

Comments are invited.

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

Phone (301) 827-3800

FAX (301) 827-4065 or write to:

FDA Veterinarian (HFV-3)
7519 Standish Place
Rockville, MD 20855

What Does the MUMS Legislation Mean? *(Continued)*

What are the criteria for determining minor use?

Frequency and geography define minor use. Minor use means that the intended use of a drug in a major species is for an indication that occurs infrequently and in a small number of animals, or in a limited geographical area and in only a small number of animals annually.

Do veterinarians really treat minor species such as earthworms, crickets, honeybees or abalone?

Yes, they do. Also, these species may be treated when they are sick, but not always by a veterinarian. Many times the owners of the animals are forced to treat them themselves to prevent disease or death. Minor species are typically treated with drugs not approved for them, because no such approved drugs exist. Although the legislation will not make drugs available for all species and for all needs, it will offer new options for drug sponsors to start developing additional products that FDA could approve or otherwise make legally available for use by veterinarians and by laypersons to treat minor species.

Why should companies and the government expend resources on keeping minor species healthy?

The effects of MUMS can go well beyond the health of individual minor species animals. Keeping these animals healthy is important for the animal's welfare, for the prevention of the spread of diseases to other animals or humans, and because these animals often provide other benefits to humans. The honeybee is a good example.

The U.S. Department of Agriculture estimates that the honeybee is responsible for 80 percent of all crop pollination in the United States. Major crops that depend on honeybees for pollination are alfalfa seed, almond, apple, avocado, blueberry, cantaloupe, cherry, cranberry, cucumber, honeydew, kiwi fruit, pear, plum, sunflower, vegetable seed and watermelon. The National Honey Board says that professional beekeepers keep about 2 million bee colonies moving from State to State every year providing pollination services. In other words, keeping the bee population healthy is essential to production of many of the crops we eat.

Will FDA play any role in determining whether research will be directed at specific minor species or uses?

Yes, but only indirectly. The new law includes a provision for making grants available for MUMS research. CVM will award grants to applicants doing research in these areas. Because it will decide how the grant money will be awarded, it will have some influence on what research will be done. However, the amount of funding available for the grant program is limited, so the overall influence will be limited.

Many times the owners of the animals are forced to treat them themselves to prevent disease or death. Minor species are typically treated with drugs not approved for them, because no such approved drugs exist.

How much will be available in grants? Who will be eligible to receive them? Who will decide who gets them?

For the first fiscal year (October 1 to September 30), the legislation authorizes $1 million for grants. The amount rises to $2 million the second year. But, even though MUMS authorizes the funds, Congress must also appropriate the funds before the grant program can be used. The first year's grants cannot be awarded until implementing regulations are written, so there will be a delay of at least 12 months while proposed rules are drafted before the grant application process can actually begin.

What is the marketing exclusivity offered under the legislation? How will it help get drugs available?

For designated drugs, this provision gives the sponsor seven years exclusivity for a specific drug indication. That market protection can give a sponsor a strong incentive to bring a product in for review because the sponsor can sell that product without competition for seven years.

One of the MUMS mechanisms is the "conditional approval." How much money will that save a sponsor? Will the large drug companies be able to take advantage of this provision?

It will not save sponsors much money in the total cost of the drug approval because they have to do everything that they would do for a regular FDA approval. The timing is what changes. It will allow the sponsor to begin generating revenue from the market for up to five years while completing the application process. Under this legislation, after a MUMS product has been shown to be safe, the company can market it while completing the effectiveness studies. CVM will continue to monitor the company's progress and can require that the company stop marketing the product at any time if progress toward completion of the approval package is unsatisfactory, or if the product is found to be ineffective or unsafe. This conditional approval mechanism could benefit any company, large or small.

(Continued, next page)

Neomycin Residue Violations Found in "Bob Veal"

The Center for Veterinary Medicine has issued a notice reminding dairy producers and others that they should not feed milk replacer products that contain neomycin to calves that could go to slaughter as veal. Federal meat inspectors at slaughter plants have reported finding a significant number of violative neomycin residues in the class of veal calves known as "bob veal."

The U.S. Department of Agriculture (USDA) defines bob veal calves as calves that are a few days to three weeks of age, weigh up to 150 lb. and do not have developed rumens, because they have been fed milk or milk-based diets only. The majority are bull calves coming directly from dairy farms. Bob veal calves make up make up about a third of the total of veal calves slaughtered, according to USDA.

Neomycin in milk replacers has been approved for treatment and control of colibacillosis (bacterial enteritis) caused by *Escherichia coli* susceptible to neomycin.

The USDA's Food Safety and Inspection Service (FSIS), which has inspectors at slaughter plants, reports illegal drug residues to FDA for follow up by field investigators. FDA conducts investigations to determine the source of the illegal residue, helps correct the problem and, when necessary, recommends possible enforcement action.

Roughly 44 percent of the 1,800 residue violations in all classes of cattle reported by FSIS in 2003 were instances of neomycin residues in bob veal. Ninety percent of these neomycin violations were in bob veal calves from Pennsylvania, New York, Maryland, Ohio and Virginia.

The likely cause of the neomycin residues is the use of medicated milk replacer containing neomycin. The dairy producer should read the label to determine if the product should be fed to calves that might be used for veal. Milk replacer with neomycin will have a label that states, "Warning**:** A withdrawal period has not been established for use in pre-ruminating calves. Do not use in calves to be processed for veal."

Dairy producers can instead use non-medicated milk replacers that have the same nutritional value as the medicated milk replacers, but do not contain neomycin. FDA recommends the use of non-medicated calf milk replacers for all calves that will be sold off the farm at an early age, including bob veal calves being held for sale by veal producers.

What Does the MUMS Legislation Mean? *(Continued)*

An outside panel will decide if sufficient safety and effectiveness data are available to place a drug on the Index, but who will decide which drugs to consider?

First of all, the Index is for products that would probably not be able to be approvable through the regular process. It is for zoo animals and exotic pets and other animals that are so varied (tropical fish), or rare (pandas), or valuable (macaws) that traditional controlled studies are just not feasible.

The potential sponsors will decide which drugs should be reviewed. It makes no sense to review drugs unless the sponsors are willing to bring them to the market. For such products, a sponsor first will ask FDA to determine whether the product is eligible for the indexing process. If so, then the sponsor can collect all pertinent information available on the product for review by a panel of experts deemed appropriate by the FDA. A report of the expert panel will be reviewed by FDA to determine whether a product may be included in the index, that is, whether it may be legally marketed without being fully approved.

Will MUMS mean that all zoo animals and others will have all the drugs they need? What do you think are the realistic limits to the effects of MUMS?

Again, the MUMS legislation was never meant to assure that all species will have all the drugs they could need. Instead, the legislation was meant to adjust or augment the approval process so that more drugs could become legally available for minor species or minor uses. The development and subsequent review of drugs for use in any species of animal is a complex, scientific undertaking that must be done in a way that complies with the law. MUMS changes the law for limited-use drugs in the hope that sponsors will be more willing and able to do the work needed to bring safe and effective drugs to the market. Other changes in legislation could help, too, as will improvements in science. The MUMS legislation is just one more improvement in the drug availability picture called for by the ADAA.

BSE Rules

FDA Prohibits Some Cattle Material in Foods, Cosmetics

The Food and Drug Administration (FDA) announced on July 9 new rules to prevent the establishment and spread of bovine spongiform encephalopathy (BSE) in the United States, including a prohibition on the use of certain material from cattle in food and cosmetics, a proposed recordkeeping requirement to support that rule, and a request for comments about possible changes to the BSE feed rule.

The changes are designed to prevent human and animal exposure to the agent that causes BSE. That agent has been linked to variant Creutzfeldt-Jakob disease in humans.

FDA announced the ban—of cattle material from FDA-regulated human food products, including dietary supplements, and from cosmetics—in the form of an Interim Final Rule that went into effect immediately upon its publication in the July 14 *Federal Register*. FDA will accept comments about it until October 12.

Under this rule, FDA prohibits the use of high-risk, cattle-derived materials that can carry the BSE agent in human food, including certain meat-based products, and cosmetics. These high risk materials include "specified risk material" (SRM), which is defined as brain, skull, eyes, trigeminal ganglia, spinal cord, vertebral column (excluding the vertebrae of the tail, the transverse processes of the thoracic and lumbar vertebrae, and the wings of the sacrum) and the dorsal root ganglia of cattle more than 30 months of age. SRMs also include the tonsils and the distal ileum of the small intestine of cattle of any age.

The rule also prohibits the use, in human food and cosmetics, of material from non-ambulatory disabled cattle, the small intestine of all cattle, material not inspected and passed for human consumption, and mechanically separated beef. Tallow that contains no prohibited cattle material or that contains no more than 0.15 percent hexane-insoluble impurities and tallow derivatives may be used in cosmetics and other food products. The insoluble impurities standard is the same as that set for protein free tallow by the Office International des Epizooties (OIE), the international animal health standard setting body.

The changes will make FDA's regulation of food products consistent with the U.S. Department of Agriculture's (USDA) regulations issued in January.

In a July 9 joint press release, FDA and USDA said their actions "will minimize human exposure to materials that scientific studies have demonstrated are likely to contain the BSE agent when derived from cattle that are infected with the disease."

To ensure compliance, the rule also requires that companies make existing relevant records available to FDA. The proposed recordkeeping rule would require manufacturers and processors of FDA-regulated human food and cosmetic products containing cattle-derived material to keep records showing that prohibited materials were not used. The companies would be required to keep their records for two years under the proposed rule.

According to Dr. Robert Brackett, Director of FDA's Center for Food Safety and Applied Nutrition, speaking during a July 9 press teleconference, the Interim Final Rule "mirrors what USDA did with meat products in January; that is, it prohibits the use of high-risk materials…in human foods, dietary supplements and cosmetics."

ANPRM

Also on July 9, FDA in conjunction with USDA, announced an Advance Notice of Proposed Rulemaking (ANPRM) that requests public comment on several additional actions the Federal government is considering regarding BSE.

FDA is requesting comment, especially scientific information, on four measures related to animal feed:

- A requirement for the removal of all specified risk materials (SRM) from all animal feed, including pet food. This measure would control the risks of cross-contamination that could occur throughout the feed manufacturing and distribution process or through misfeeding on the farm.
- A requirement that anyone handling and storing feed and ingredients during manufacture and shipment has separate equipment or facilities for prohibited and non-prohibited material to prevent cross-contamination.
- A prohibition of the use of all mammalian and poultry protein in ruminant feed to prevent cross-contamination.

(Continued, next page)

BSE INSPECTION UPDATE

FDA Reports Latest BSE Inspection Figures

As of July 17, the Food and Drug Administration (FDA) had received more than 31,000 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 70 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

(Continued, next page)

BSE Rules

FDA Prohibits Some Cattle Material . . . (Continued)

- A prohibition against the use of materials from non-ambulatory disabled cattle and dead stock in all animal feed.

The ANPRM also includes a report on the work of the International Review Team (IRT, convened by Agriculture Secretary Veneman to review the U.S. actions in response to the case of BSE in the United States) along with a summary of the many actions already taken by each agency on BSE.

In the ANPRM, USDA's Food Safety and Inspection Service is asking for comments on actions it took earlier to protect against BSE in the human food supply. In addition, it is asking whether a country's BSE status should be taken into account when USDA determines whether a country's meat inspection system is equivalent to the U.S. regulations.

USDA's Animal and Plant Health Inspection Service (APHIS) is specifically seeking comments on the implementation of a national animal identification system. In April, USDA announced the availability of $18 million in Commodity Credit Corporation funding to expedite development of a national animal identification system, which is currently underway. APHIS is inviting comments on when and under what circumstances the program should move from voluntary to mandatory, and which species should be covered now and over the long term.

SRM Ban

In announcing the ANPRM, FDA said that it "has reached a preliminary conclusion that it should propose to remove SRMs from all animal feed (including pet food) and is currently working on a proposal to accomplish this goal."

The key benefit to prohibiting all SRMs from all feed would be that it would prevent all possible cross-contamination between ruminant and non-ruminant feed. The IRT cited evidence in the United Kingdom that shows the dangers of cattle infection that can be caused by the cattle consuming feed that was accidentally contaminated when manufactured in premises that legitimately used mammalian meat and bone meal in feed for pigs and poultry. The IRT also cited an ongoing study at the Veterinary Laboratories Agency in the United Kingdom that shows transmission of BSE with a significantly lower dose of infectious brain tissue than previously thought. Further, the Harvard-Tuskegee Study showed that removing SRMs from all animal feed reduces the potential exposure of cattle to the BSE agent by 88 percent, assuming 10 BSE infected cattle were introduced into the United States.

An SRM ban in all feed could eliminate the need for some other actions previously announced by FDA, such as a potential ban on the use of poultry litter in cattle feed.

FDA Reports Latest BSE Inspection Figures *(Continued)*

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 July 17.)

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** – 244
- **Number of active firms handling materials prohibited from use in ruminant feed** – 161 (66 percent of those active firms inspected)
- **Of those 161 firms:**
  - ❖ 0 were classified as OAI
  - ❖ 4 (2.5 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** – 1,081
- **Number of active firms handling materials prohibited from use in ruminant feed** – 367 (34 percent of those active firms inspected)
- **Of those 367 firms:**
  - ❖ 3 (0.8 percent) were classified as OAI
  - ❖ 5 (1.4 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** – 5,059
- **Number of active firms handling materials prohibited from use in ruminant feed** – 1,358 (27 percent of those active firms inspected)
- **Of those 1,358 firms:**
  - ❖ 6 (0.4 percent) were classified as OAI
  - ❖ 36 (2.7 percent) were classified as VAI

Protein blenders

These firms blend rendered animal protein to produce feed ingredients 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 percent of those active firms inspected)
- **Of those 67 firms:**
  - ❖ 1 (1.5 percent) was classified as OAI
  - ❖ 2 (3.0 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** – 6,452
- **Number of active renderers, feed mills, and protein blenders processing with prohibited materials** – 556 (8.6 percent of those active firms inspected)
- **Of those 556 firms:**
  - ❖ 8 (1.4 percent) were classified as OAI
  - ❖ 19 (3.4 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** – 10,915
- **Number of active firms handling materials prohibited from use in ruminant feed** – 2,205 (20 percent of those active firms inspected)
- **Of those 2,205 firms:**
  - ❖ 16 (0.7 percent) were classified as OAI
  - ❖ 76 (3.4 percent) were classified as VAI

Total Firms

- **Number of active firms whose initial inspection has been reported to FDA** – 14,355
- **Number of active firms handling materials prohibited from use in ruminant feed** – 2,901 (20 percent of those active firms inspected)
- **Of those 2,901 firms:**
  - ❖ 17 (0.6 percent) were classified as OAI
  - ❖ 86 (3.0 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.)

FDA Validates Rapid Screening Tests for Antibiotics in Milk

by Philip James Kijak, Team Leader, Analytical Methods Team, Office of Research

This article is based on a presentation the author made at the 2004 Mid-Atlantic States Conference for Bovine Practitioners sponsored by the Maryland Veterinary Medical Association on March 25, 2004.

The ability of regulators in the United States to test every load of milk sold for the presence of antibiotics is a complex regulatory and technical achievement, supported by the Food and Drug Administration's (FDA) ability to test the milk screening test.

A national conference made up of State and Federal food regulators initiated the testing requirement in 1991. The regulators, along with representatives of the farmers, dairy industry and consumer groups, are organized as the National Conference on Interstate Milk Shipments (NCIMS). The purpose of the NCIMS is to develop regulations used by the States for Grade A milk and milk products in interstate commerce. The NCIMS developed the requirement that all tankers of milk in the United States be screened for residues of penicillin and other beta-lactam antibiotic drugs.

The only way to comply with that requirement, while at the same time not unduly delaying the delivery of milk, is through the use of highly accurate rapid screening tests. The United States had many commercial tests available, but did not have any program in place to determine whether these tests were suitable for use in a regulatory program. This is where FDA plays its role. NCIMS requested FDA to develop a program to validate these rapid screening tests for regulatory use.

FDA developed a validation program for test kits through a cooperative effort with the AOAC Research Institute. AOAC International, formerly known as the Association of Official Analytical Chemists, operates its Research Institute to provide independent certification on the performance of various commercial rapid screening tests. Under this program, FDA uses testing both by the kit manufacturer and an independent laboratory to determine the suitability of the kits for regulatory use.

In order to be considered for regulatory uses, a test kit must be able to detect—at or below the legal tolerance (safe level)—four of the six beta-lactam type antibiotic drugs commonly used in dairy cows. The six beta lactam drugs are ampicillin, amoxicillin, ceftiofur, cephapirin, cloxacillin and penicillin G.

In addition, all new tests must be capable of giving a printed record that includes the sample identification, date, time, operator, kit lot and result. When the program was first started, FDA would accept tests that required an operator to visually interpret the results and determine whether the milk was safe. Problems found with the use of the visually read tests led to the requirement in the late 1990s that all new test must be read by an instrument.

Sensitivity, selectivity

If a test can meet the preliminary requirements, then the primary focus of the validation is a test kit's sensitivity and selectivity.

Sensitivity relates to the possibility of false negatives and selectivity to the possibility of false positives.

Sensitivity is the ability to detect a specific beta-lactam drug in milk. To calculate a test kit's sensitivity, the independent laboratory tests a statistically significant number of samples of the test kit over a range of drug concentrations up to the tolerance level. The researchers are trying to determine the concentration of the drug at which the kit gives a positive result 90 percent of the time with 95 percent confidence (90/95). In other words, the test must be correct with 90 percent of the samples 95 percent of the time. The researchers run this test with each type of beta-lactam drug that the kit should be able to detect.

Selectivity is determined by the response of the kit to truly drug-free milk. To be acceptable, a kit must not give more than two positive readings for 60 known negative samples.

Researchers then do additional studies to be sure the test kits work properly when used in the field. One study is designed to determine the ruggedness of the kit. It evaluates the effect of slight changes to operating conditions, such as specified temperature, volumes and times, that would be expected under typical use of the test kit. Another study is designed to find out if the kits will give false positives or negatives when other veterinary drugs that might be used in dairy cows are in the milk. Additional studies test the performance of the kit when high levels of somatic cells or bacteria are present in the milk.

Label

The kit manufacturer must include information that the researchers gather during the validation tests about sensitivity, selectivity, drug interference and other key findings in the instructions for use included with the kit, referred to as the kit label. This information makes

(Continued, next page)

FDA Validates Rapid Screening Tests... *(Continued)*

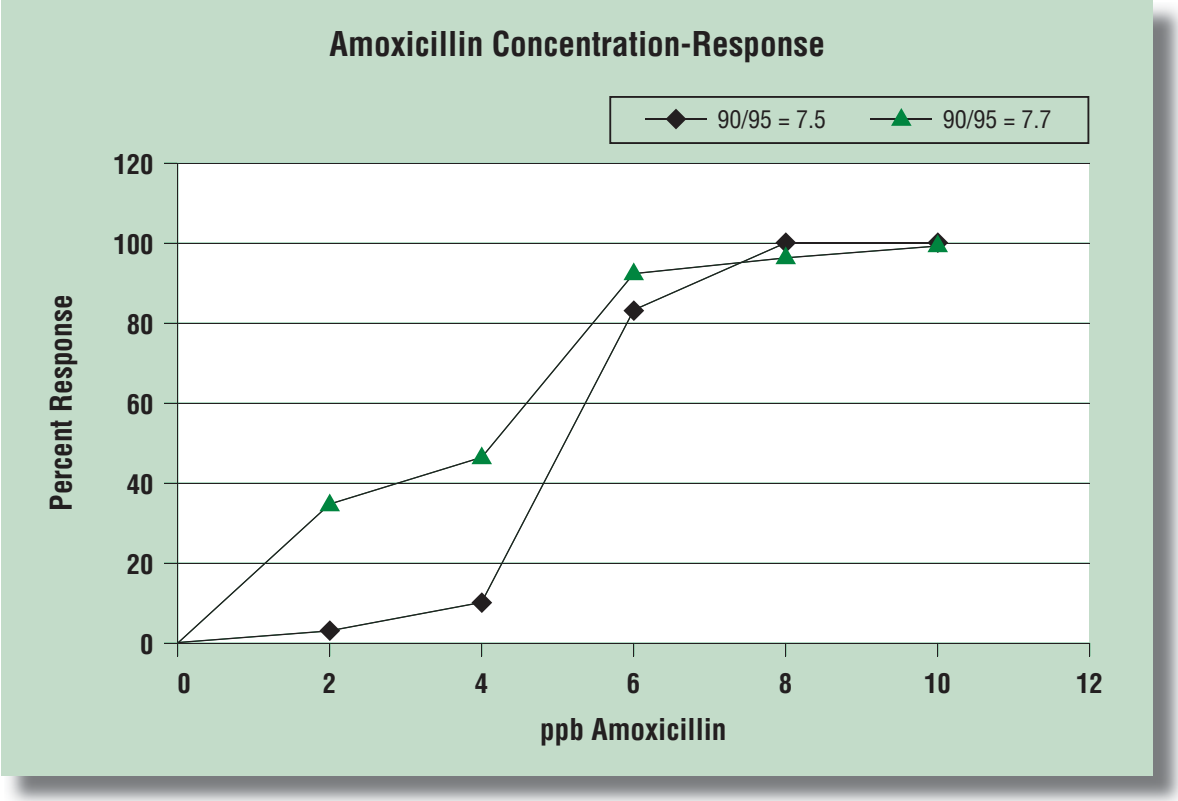


Figure 1. Concentration response curves of two test kits to amoxicillin showing the difference in the kits' response.

the kit label the most important resource to the user when determining the appropriate kit to use.

The label includes both the calculated 90/95 concentration for each drug claimed and information on the response of the kit at specific drug concentrations. Both pieces of information are important in evaluating the sensitivity of a kit to a specific drug.

In the example in Figure 1, the concentration response curves to amoxicillin for two test kits are shown. The calculated 90/95 concentrations for the two kits are almost identical.

Yet, at low concentrations, the kit described by triangles gives a significantly greater percentage of positive samples.

The difference in sensitivity at low concentrations is documented in the label information. The respective sections of the label for each kit are shown in the second figure.

By reading and using the label information, the test kit users can make an informed decision about the suitability of a kit for their application. For example, if a milk producer wants to screen the bulk tank before pickup to ensure that it is not positive, the producer would want the most sensitive test possible.

(Continued, next page)

Drug Concentration (ppb)	*Amoxicillin*	*Drug Concentration (ppb)*	*Amoxicillin*
		1	
1	3	2	33
3		3	
4	10	4	47
5		5	
6	83	6	93
8	100	8	97
10	100	10	100
14		14	
20		20	
Tolerance Safe Level (ppb)	10	**Tolerance Safe Level (ppb)**	10
90/95% Concentration (ppb)	7.5	**90/95% Concentration (ppb)**	7.7

Figure 2. Examples of how the drug concentration response information shown in figure 1 is listed on the test kit label for both test kits.

FDA Validates Rapid Screening Tests... *(Continued)*

Additional information required to be on the kit label includes a list of drugs known to cause either false positives or false negatives when present in the milk, information on the selectivity of the kit, and any other potential limitations to the performance of the kit that were discovered during the validation process.

Retest programs

The user of the test kit needs to be aware that the kits do have limitations.

Because the 90/95 concentration must be at or below the tolerance/safe level, the kits will always have the potential to give a false violative result, meaning that, although the drug is present and the kit indicated a violation, the concentrations is not at a level that would be in violation of the safety standards.

To minimize the consequence to the milk producer from a test kit's false positive results, NCIMS calls for two retests of a sample before the milk is condemned. The initial retest is done using the same test as the one used for the initial screening. This retest is done in duplicate with the positive sample and a negative control sample. If either of the duplicate tests gives a positive result and the results for the positive and negative control are correct, the tanker load is a "presumptive positive." Then a second retest is done.

This second retest is also done in duplicate along with positive and negative control samples. The second retest sample must be tested in a State or State certified laboratory, and may be done using a different test kit. If either of the second retests is positive, the result is called a screening test positive, and the milk considered to be adulterated with beta-lactam residues.

The effect of the retest program is to greatly decrease the likehood of false positive results. For example, if a kit had a false positive rate of 1 in 1,000, the probability of a negative sample being positive for both the initial screen in the first retest is 1 in 500,000. If the same test is used for the second retest, the chances are only 1 in 250 million that true negative milk will be declared screening test positive.

The retesting also decreases the probability that milk with a beta-lactam drug present will test positive when the antibiotic's concentration is below the tolerance level. However, the effect is largely dependent on the concentration of the drug in the milk. At drug concentrations where the test kit usually gives a positive result, a negative retest is highly unlikely. But as drug concentration in the milk decreases to the point where the kit gives negative results, the probability that the retest will give a negative result also increases.

No information about amount of drug

Even though modern kits present printouts that typically include numeric results, they often do not offer information about the amount of drug present. This printout does not actually give a good idea of the level of drug present, because of the test-to-test variability of most test kits.

Figure 3 shows some results obtained of a test kit's response to amoxicillin. The kit was functioning properly, and all negative results are well below the zero line. And at drug concentrations at tolerance and above, the result is always positive. However, there is a great range of actual readings obtained at any single concentration. For example, several of the high readings at 5 parts per billion (ppb) are well within the typical range of readings obtained at 12 ppb. If a user were to test milk with this test, and get a reading of 4 ppb, the drug concentration in the milk could be less than 5 ppb, greater than 12 ppb, or somewhere in between.

The sensitivity of the kit to each drug that the kit can detect for is different. This variability prevents the use of the test kit's numeric readout to determine the drug concentration in the milk.

(Continued, next page)

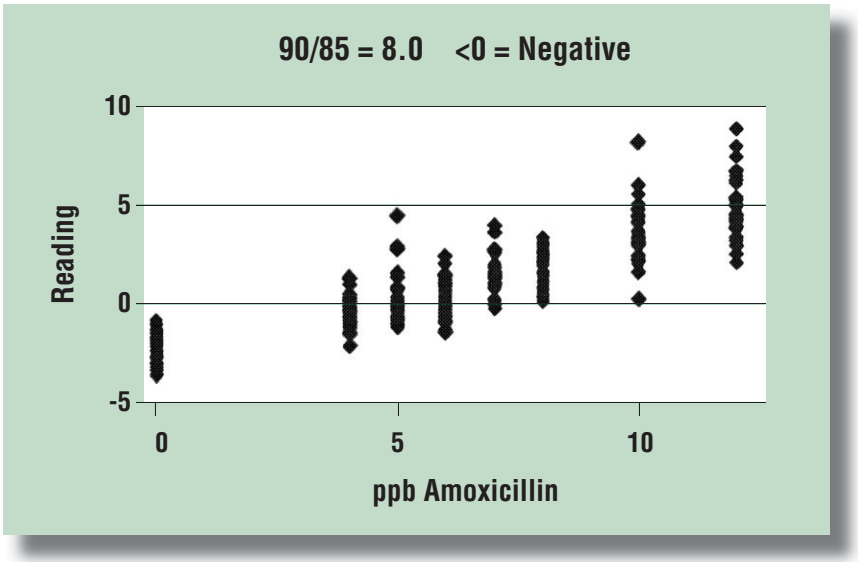


Figure 3. Results of test kit's response to amoxicillin showing why screening tests cannot be used to show drug concentration.

FDA Validates Rapid Screening Tests... *(Continued)*

Limitations

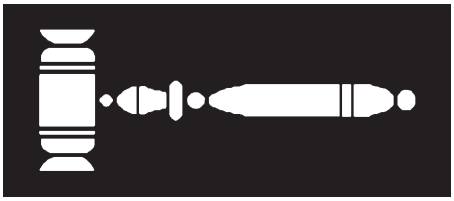
The screening tests are meant to be fast and accurate. They are not meant to supply complete information about the potential of antibiotics in milk.

For instance, most kits will not test for all six beta-lactam drugs. And, in most cases, the tests do not provide information on what drug caused the positive result.

Still, the screening tests fulfill their principal duty—keeping the milk supply in the United States safe—while not slowing down delivery of fresh milk to consumers.

Regulatory Activities

by Marilyn Broderick, CVM Communications Staff



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

- Andrew E. Brown, Owner, Brown's Livestock, Winchester, Va.
- John and Rusty Eaker, Co-Owners, Eaker Dairy, Cherryville, N.C.
- Albert J. Huizenga, Owner, Fir Crest Hauling, Lynden, Wash.
- Jake A. and Lori A. Slegers, Co-Owners, Jake Slegers Jr. Dairy, Pixely, Calif.
- Juan Manuel Barreto, Owner, J.M. Dairy Corporation, Arecibo, P.R.
- Kenneth Deputy, Owner, Mammoth Cave Dairy Auction, Inc., Smiths Grove, Ky.
- Manuel F. and Mary F. Barcelos, Co-Owners, M & M Barcelos Dairy, Chowchilla, Calif.
- William F. Nickle, North East, Md.
- Perry T. Dewey, Owner, Perry Dewey Farm, Clymer, N.Y.
- John C. Reynolds, Swanton, Vt.
- Michael J. Arambel, Manager, Sunstar Dairy, Rupert, Idaho
- Duaine E. and Kenneth D. Walker, Co-Owners, Walker Farms, Minerva, Ohio

The above violations involved neomycin in bob veal calves, penicillin in dairy cows, neomycin and sulfadimethoxine in a cow, gentamicin in dairy cows and sulfadimethoxine in a dairy cow.

Warning Letters were issued to the following because investigations into illegal tissue residues in animals sold for slaughter as human food revealed serious deviations from the regulations for Extralabel Drug Use in Animals. These deviations caused an animal drug to be used in a manner that was unsafe and adulterated under the Federal Food, Drug, and Cosmetic Act.

- Jack Davis, President, Idacrest Farms, Inc., Kuna, Idaho
- Mike Loy, Columbia, Ky.
- Charles H. Stewart, Owner, Stewart's Dairy, Addison, N.Y.
- Timothy Devine, Co-Owner, Devine Farms, LLC, Canastota, N.Y.
- Allan B. Thomas, Owner, Enumclaw, Wash.
- James J. Ostrom, President and CEO, Milk Source, LLC, Kaukauna, Wis.
- David J. Boor, Owner, Boor Crest Farm, Horseheads, N.Y.
- Allen L. Van Nurden, Co-Owner, Allen & Dale Van Nurden Farm, Rice, Minn.

The above violations involved penicillin and sulfadimethoxine in a culled dairy cow, gentamicin in a dairy cow, neomycin in a bob veal calves, flunixin and sulfonamide in dairy cows and sulfadimethoxine in a dairy cow.

A Warning Letter was sent to Henry M. Nelson, President, Nelsons Premix Service, Inc., Storm Lake, Iowa, because an inspection of the veterinary health products sales facility revealed the firm purchased and further distributed prescription drug products for animal use without an order from a licensed veterinarian and without adequate directions for use. Selling new animal drugs with "adequate directions for use" means adequate directions for which the layman can use a drug safely and for the purposes for which it was intended. Such adequate directions for use by laypersons cannot be written for prescription drugs because the drugs can be used safely only at the direction of, and under the supervision of, a licensed veterinarian. Dispensing of a prescription drug other than by or upon the lawful written or oral order of a licensed veterinarian results in the drug being misbranded.

Warning Letters were received by Dwight Armstrong, President and CEO, North American Nutritional Companies, Inc., Lewisburg, Ohio; and by Ronald M. Foster, Randall C. Boyce, Trevor O. Foster and George P. Foster, Managers, Fresno Farming LLC, Livingston, Calif., for significant deviations from the requirements set forth in Title 21 Code of Federal Regulations (CFR), Part 589.2000 - Animal Proteins Prohibited in Ruminant Feed.

(Continued, next page)

Regulatory Activities *(Continued)*

This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy. The inspection at American Nutritional Companies, Inc., revealed that the firm failed to maintain written procedures for separating products that may contain protein derived from mammalian tissues from all other protein products from the time of receipt until the time of shipment. Specifically, the firm received poultry digest that listed a prohibited ingredient and that contained the label statement, "Warning: Do Not Feed to Cattle or Other Ruminants," but had no written procedures to ensure that ruminant feed was not cross-contaminated with prohibited material. The inspection at Fresno Farming, LLC, revealed failure to provide for measures to avoid commingling or cross-contamination of products that contain or may contain protein derived from mammalian tissues into animal protein or feeds that may be used for ruminants; failure to maintain written procedures specifying the clean-out procedures and specifying the procedures for separating products that contain or may contain protein derived from mammalian tissue from all other protein products; and failure to maintain records sufficient to track prohibited materials throughout their distribution.

A Warning Letter was issued to Randall Copeland, Executive Vice-President of Operations, Menu Foods, Inc., Pennsauken, N.J., because an inspection of the animal feed manufacturing operation found a failure to label canned animal food that contains protein sources of bovine origin including beef lung with the cautionary statement "Do Not Feed to Cattle or Other Ruminants" in violation of Title 21 CFR Part 589.2000.

A Warning Wetter was issued to David W. Bernauer, CEO and Chairman of the Board, Walgreen Company, Deerfield, Ill., because an inspection of the firm's warehouse in Mt. Vernon, Ill., revealed numerous insanitary conditions that caused the food and drug products there to be adulterated and pet food products that contain or may contain animal protein prohibited ruminant feed were salvaged, repackaged, and donated without bearing the cautionary statement "Do Not Feed to Cattle or Other Ruminants."

Comings and Goings

New Hires

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Virginia Recta, Math Statistician
- Elizabeth Canter, Information Management Specialist
- Kendra Biddick, Consumer Safety Officer

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Janice Derr, DVM, Veterinary Medical Officer

OFFICE OF MANAGEMENT

- Lisa Durphy, Personnel Management Analyst
- David Lynch, Operations Research Analyst

OFFICE OF RESEARCH

- Lisa Rojas, Biological Science Lab Technician
- Richard Cullison, DVM, Veterinary Medical Officer

FDA Announces FY 2005 Animal Drug User Fee Rates

The Food and Drug Administration (FDA) published a notice in the August 2 *Federal Register* announcing rates for animal drug application, product, establishment and sponsor fees for Fiscal Year (FY) 2005, as authorized under the Animal Drug User Fee Act of 2003 (ADUFA).

The Act authorizes FDA to establish and collect user fees that are used to enhance the performance of the animal drug review process.

ADUFA provides a formula for adjusting fees based on increases in costs due to inflation or changes in workload. The notice provides details about the formulas FDA used to calculate the rates. It also explains payment procedures.

The law permits FDA in FY 2005 to collect up to $2,088,400 in fees under each of the four categories, for a total of $8,353,600. That figure represents a $2,000,000 base per category that is adjusted to reflect a 4.42 percent increase in inflation. FDA also calculated a workload adjuster, but found that it does not alter the fee amount.

For FY 2005, the fee is $119,300 for each animal drug application and $59,650 for a supplemental animal drug application for which safety or effectiveness data are required. The annual product fee is $3,085, the annual establishment fee is $42,600, and the annual sponsor fee is $32,150. FDA will not accept an application for filing unless the sponsor has paid all the fees it owes.

The notice also provides procedures animal drug sponsors should use to pay the FY 2005 fees. The application fee rates are effective for applications received by CVM from October 1, 2004, until September 30, 2005. FDA will issue invoices for all other FY 2005 fees by December 30, 2004. Payments will be due January 31, 2005.

International Activities

FDA, NRSP-7 to Sponsor International Workshop on Minor Species/Use

The Food and Drug Administration (FDA), in cooperation with the U.S. Department of Agriculture's minor use research program, the National Research Support Project #7 (NRSP-7), will sponsor a public workshop October 7- 8 in Rockville, Md., on international issues concerning the development and approval of drugs for minor uses and minor species, also known as MUMS drugs.

According to FDA's announcement of the workshop, its purpose "is to assemble international expertise to discuss the global pursuit of drug approvals for MUMS" drugs. The workshop is designed to provide opportunities for discussion of the global perspectives for MUMS drug needs and approvals.

Specific topics to be addressed include:

- Data requirements for MUMS approvals (such as effectiveness, target animal safety, human food safety, environmental safety);
- The classification of minor species; and
- Husbandry practices in various regions of the world.

The organizers hope that the workshop will generate methods and strategies to improve cooperation and coordination of programs to help MUMS drug approvals internationally.

Details

Meeting: International Workshop on Minor Use and Minor Species (MUMS): A Global Perspective

Date and time: October 7, from 9 a.m. to 5 p.m.; October 8, from 9 a.m. to 1 p.m.

Location: DoubleTree Hotel, Plaza Room III, 1750 Rockville Pike, Rockville, Md., 20852

Registration: Forms are available through the Center for Veterinary Medicine's website at *http://www.fda.gov/cvm* or on the NRSP-7 website at *http://www.nrsp7.org*. Because seating is limited, to attend you must register online or submit a registration form by October 6, 2004, to Ms. Anna Roy, Center for Veterinary Medicine, Food and Drug Administration, (HFV-6), 7519 Standish Place, Rockville, Md., 20855; 301-827-2957; fax 301-827-4572; or E-mail *aroy@cvm.fda.gov*.

Registration fee: None

Contact person: Dr. Margaret Oeller, Center for Veterinary Medicine, Food and Drug Administration, (HFV-1), 7519 Standish Place, Rockville, Md., 20855; 301-827-3067; fax 301-827-4401; E-mail *moeller@cvm.fda.gov*.

APPROVALS FOR MAY AND JUNE 2004

New Animal Drug Approvals

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Boehringer Ingelheim Vetmedica, Inc. (NADA 141-228)	N-butylscopolammonium bromide (Buscopan Injectable Solution)	Horses. For the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic and simple impactions in horses.	**INJECTABLE**—The NADA provides for the veterinary prescription use of a solution of N-butylscopolammonium bromide by intravenous injection for the control of abdominal pain (colic) associated with spasmodic colic, flatulent colic, and simple impactions in horses. *Federal Register* 06/25/04

(Continued, next page)

Supplemental New Animal Drug Approvals *(Continued)*

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Intervet, Inc. (NADA 141-236)	Porcine zinc insulin (Vetsulin Suspension)	Dogs. For the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus.	**INJECTABLE**—The NADA provides for the veterinary prescription use of an injectable suspension of zinc insulin of porcine origin for the reduction of hyperglycemia and hyperglycemia-associated clinical signs in dogs with diabetes mellitus. *Federal Register* 05/10/04

Supplemental New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Fort Dodge Animal Health, Division of Wyeth (NADA 141-087)	Moxidectin 2.0% (Quest Gel)	Horses. For the treatment and control of various species of internal parasites in horses and ponies.	**ORAL**—The supplemental NADA provides for the addition of one new species of adult small strongyle and for the speciation of adult small strongyles. *Federal Register* 05/05/04
Merial Ltd. (NADA 140-833)	Ivermectin and Clorsulon (Ivomec Plus Injection)	Cattle. For the protection from re-infection with three species of internal parasites following administration.	**INJECTABLE**—The supplemental NADA provides for an increased period of protection by extending the period of persistent effectiveness for *Oesophagostomum radiatum* to 28 days after treatment, and for *Cooperia punctata* and *Trichostrongylus axei* to 21 days after treatment. 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* 06/07/04
Phibro Animal Health (NADA 008-804)	Oxytetracycline (TM-50, TM-5OD, TM-100, TM-100D Type A Medicated Articles)	Calves, beef cattle and nonlactating dairy cattle. Type A medicated articles to be used for making medicated feeds for the treatment of various bacterial diseases of livestock.	**MEDICATED FEED**—The supplemental NADA provides for a 0-day withdrawal time prior to slaughter when Type C medicated feeds containing oxytetracyline are fed continuously to calves, beef cattle and nonlactating dairy cattle at a dosage of 10 milligrams per pound of body weight for up to 14 days. *Federal Register* 05/19/04
Phibro Animal Health (NADA 095-143)	Oxytetracycline (Terramycin 50, Terramycin 100, and Terramycin 200 Type A Medicated Articles)	Calves, beef cattle and nonlactating dairy cattle. Type A medicated articles to be used for making medicated feeds for the treatment of various bacterial diseases of livestock.	**MEDICATED FEED**—The supplemental NADA provides for a 0-day withdrawal time prior to slaughter when Type C medicated feeds containing oxytetracyline are fed continuously to calves, beef cattle and nonlactating dairy cattle at a dosage of 10 milligrams per pound of body weight for up to 14 days. *Federal Register* 05/19/04

Abbreviated New Animal Drug Approvals

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Pennfield Oil Company (ANADA 200-359)	Chlortetracycline and decoquinate (Pennchlor and Deccox)	Calves, beef and nonlactating dairy cattle. For the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*; for treatment of bacterial enteritis caused by *Escherichia coli*; for bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline.	**MEDICATED FEED**—The ANADA provides for the use of single-ingredient, chlortetracycline and decoquinate Type A medicated articles to make two-way combination drug Type B and Type C medicated feeds. Pennfield Oil Company's Pennchlor and Deccox is approved as a generic copy of Alpharma, Inc.'s NADA 141-147. *Federal Register* 05/13/04
Veterinary Laboratories, Inc. (ANADA 200-341)	Ivermectin (Sparmectin-E)	Horses. For the treatment and control of various species of internal and cutaneous parasites.	**ORAL**—The ANADA provides for oral use of Sparmectin-E Liquid for horses for the treatment and control of various species of internal and cutaneous parasites. Veterinary Laboratories' Sparmectin-E Liquid for Horses is approved as a generic copy of Merial Ltd.'s NADA 140-439. *Federal Register* 05/05/04
Pennfield Oil Company (ANADA 200-356)	Chlortetracycline hydrochloride and tiamulin hydrogen fumarate (Pennchlor and Denagard)	Swine. For the treatment of swine bacterial enteritis caused by *Escherichia coli* and *Salmonella choleraesuis* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline, and control of swine dysentery associated with *Brachyspira* (formerly *Serpulina* or *Treponema*) *hyodysenteriae* susceptible to tiamulin.	**MEDICATED FEED**—The ANADA provides for the use of single-ingredient Type A medicated articles containing tiamulin hydrogen fumarate and chlortetracycline hydrochloride to make two-way combination drug Type B and Type C medicated feeds for swine. Pennfield Oil Company's Pennchlor and Denagard is approved as a generic copy of Boehringer Ingelheim Vetmedica, Inc.'s NADA 141-011. *Federal Register* 06/08/04
Boehringer Ingelheim Vetmedica, Inc. (ANADA 200-361)	Acepromazine maleate injection (Acepromazine Maleate Injection)	Dogs, cats, and horses. For use as a tranquilizer.	**INJECTABLE**—The ANADA provides for the veterinary prescription use of acepromazine maleate injectable solution in dogs, cats and horses as a tranquilizer. Boehringer Ingelheim Vetmedica's Acepromazine Maleate Injection is approved as a generic copy of Fort Dodge Animal Health's Promace Injectable approved under NADA 015-030. *Federal Register* 06/17/04
Cross Vetpharm Group Ltd. (ANADA 200-317)	Dexamethasone sodium phosphate (Dexium-SP Injectable Solution)	Horses. A rapid adrenal glucocorticoid and/or anti-inflammatory agent.	**INJECTABLE**—The ANADA provides for the veterinary prescription use of dexamethasone sodium phosphate injectable solution as a rapid adrenal glucocorticoid and/or anti-inflammatory agent in horses. Cross Vetpharm Group Ltd.'s Dexium-SP is approved as a generic copy of Steris Laboratories, Inc.'s Dexamethasone Injection, approved under NADA 104-606. *Federal Register* 06/18/04

(Continued, next page)

Abbreviated New Animal Drug Approvals *(Continued)*

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Phoenix Scientific, Inc. (ANADA 200-193)	Clindamycin Hydrochloride Oral Liquid (Clindamycin Hydrochloride Oral Liquid)	Cats and dogs. For the treatment of certain bacterial diseases.	**ORAL**—The supplemental ANADA provides for an expanded dose range and revised indications for the use of clindamycin hydrochloride oral liquid in both dogs and cats for the treatment of certain bacterial diseases. *Federal Register* 06/07/04
Phoenix Scientific, Inc. (ANADA 200-298)	Clindamycin hydrochloride capsules (Clindamycin Hydrochloride Capsules)	Dogs. For the treatment of certain bacterial diseases.	**ORAL**—Two supplemental ANADAs were filed. One supplemental ANADA provides for an expanded dose range and revised indications wording for the oral use of clindamycin hydrochloride capsules in dogs for the treatment of certain bacterial diseases. The other supplemental ANADA provides for the use of a 300-milligram capsule size. *Federal Register* 06/09/04

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Official Business
Penalty for Private Use $300

PRESORTED STANDARD
POSTAGE AND FEES PAID
TEMPLE HILLS, MD
PERMIT NO. 4004

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

04-3147