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FDA VETERINARIAN

FDA/CVM PROPOSES TO WITHDRAW POULTRY FLUOROQUINOLONES APPROVAL

The Food and Drug Administration's Center for Veterinary Medicine is proposing to withdraw approval of the new animal drug application (NADA) for use of the fluoroquinolone antimicrobial enrofloxacin in poultry. Therefore, as required by FDA regulations, the Center has issued a notice of opportunity for a hearing on its proposal.

The Office of the Federal Register put the notice on public display October 26, 2000, and published the notice in the October 31, 2000, *Federal Register*. The document is also available through FDA's Dockets Management Branch, at *http://www.fda.gov/OHRMS/DOCKETS/98fr/cv0076.pdf*

This action is based on the Center's determinations that:

1. The use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter*, a pathogen to humans, in poultry;
2. This fluoroquinolone-resistant *Campylobacter* is transferred to humans and is a significant cause of the development of fluoroquinolone-resistant *Campylobacter* infections in humans; and
3. Fluoroquinolone-resistant *Campylobacter* infections are a hazard to human health.

The Center is proposing to withdraw the approval for use of enrofloxacin in poultry on the grounds that new evidence shows the product has not been shown to be safe.

The following approval is affected by this notice:

Enrofloxacin. NADA 140-828, Baytril® 3.23% Concentrate Antimicrobial Solution, approved October 4, 1996, 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, Bayer Corp., Agriculture Division, Animal Health, Shawnee Mission, KS.

The notice also refers to the approvals of NADAs 141-017 and 141-018 for use of *sarafloxacin hydrochloride* in poultry. Abbott Laboratories, North Chicago, IL, is the sponsor of these NADAs. NADA 141-017, Sara Flox® WSP, was approved August 18, 1995, for the control of mortality in growing turkeys and broiler chickens associated with *E. coli* organisms. NADA 141-018, Sara Flox® Injection, was approved October 12, 1995, for the control of early chick mortality associated with *E. coli* organisms in chickens and turkeys. The notice states that Abbott Laboratories has requested withdrawal of these

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FDA AND USDA SPONSOR FOOD SAFETY MEETING

by Jon F. Scheid

The Department of Health and Human Services' Food and Drug Administration (FDA) joined with the U.S. Department of Agriculture (USDA) and several livestock producer and allied groups in sponsoring a two-day meeting on how on-farm production practices can affect food safety. The meeting, "National Conference on Animal Production and Food Safety," was held September 6-7, in St. Louis, Missouri. USDA's Food Safety and Inspection Service (FSIS) organized the meeting.

The audience included more than 250 representatives of major trade associations for food animal producers, and State and Federal Government agencies. (see complete list of sponsors below)

The purpose of the meeting was to give the producer representatives a chance to report on the steps taken on farms to improve food safety, and to discuss with Government officials their ideas of research that still needs to be done. A similar meeting was held five years ago, and this year's meeting built on the information from the earlier meeting.

In a few months, USDA and FDA's Center for Veterinary Medicine (CVM) will post the complete proceedings from the 2000 meeting on their

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NADAs, that by doing so, the company has waived its right to a hearing and therefore, these NADAs are not covered by the notice.

Enrofloxacin belongs to the class of antimicrobial drugs called fluoroquinolones. Fluoroquinolones also are approved for use in humans, and they are considered to be one of the most valuable antimicrobial drug classes available to treat human infections because of their spectrum of activity, safety, and ease of administration. This class of drugs is effective against a wide range of human diseases and is used both in treatment and prophylaxis of bacterial infections in the community and in hospitals. Fluoroquinolones are used routinely by physicians for the treatment of foodborne disease. These diseases have a major public health consequence in the United States.

FDA approved the NADAs for fluoroquinolones for use in poultry in 1995 and 1996. At the time of approval, the Center instituted several strategies intended to prevent or mitigate the development of resistance. However, resistance developed to the fluoroquinolones in *Campylobacter*, a major foodborne pathogen in humans.

After thoroughly analyzing all the data and evidence, the Center has determined that:

1. The primary cause of the emergence of domestically acquired fluoroquinolone-resistant *Campylobacter* infections in humans is the consumption of or contact with contaminated food;
2. Poultry are a predominant source of campylobacteriosis in humans;
3. Poultry carrying fluoroquinolone-resistant *Campylobacter* are the predominant source of fluoroquinolone-resistant campylobacteriosis in humans; and
4. The administration of fluoroquinolones to chickens leads to development of fluoroquinolone-resistant *Campylobacter* in chickens.

The Center's conclusions are based on data from the National Antimicrobial Resistance Monitoring System (a national surveillance program operated by the Center in cooperation with the Centers for Disease Control and Prevention and the U.S. Department of Agriculture), published literature, and other sources. The data indicate that the use of fluoroquinolones in poultry is a significant cause of fluoroquinolone-resistant *Campylobacter* on poultry carcasses, and therefore a significant cause of fluoroquinolone-resistant *Campylobacter* infections in humans. The Center's conclusions are supported by data establishing a temporal association between the approvals of these drugs for use in poultry in the United States and the increase in resistant *Campylobacter* infections in humans.

Fluoroquinolones have been available for human use since 1986 and are commonly prescribed for persons with gastrointestinal illness. Yet resistance to fluoroquinolones did not increase among *Campylobacter* organisms until 1996 and 1997, soon after the approval and use of these drugs in poultry. Fluoroquinolone-resistant *Campylobacter* (including *C. jejuni*) infections in humans had reached 13.6% by 1998 and rose to 17.6% (for *C. jejuni* alone) in 1999.

Individuals or companies covered by the notice must submit a request for a hearing within 30 days following the publication of the notice of opportunity for a hearing in the *Federal Register*. Also, they must submit within 60 days following the publication of the notice all data and analysis they are using to base their request for a hearing. Other interested parties may also submit comments on the notice. Requests for a hearing or to appear at a hearing, data, and analysis, and other comments are to be identified with Docket No. 00N-1571 and must be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Refer to the October 31, 2000, *Federal Register* for the exact dates and other details. □

FDA AND USDA SPONSOR . . . (Continued)

Websites. Meanwhile, USDA and FDA will begin posting copies of many of the presentations and other information on their Websites (*www.usda.gov* and *www.fda.gov/cvm*).

The first day of the meeting included presentations describing the state of animal production and how it relates to food safety. CVM Director Dr. Stephen Sundlof presented the Government's perspective on the issue of food safety. He explained that FDA's ultimate responsibility is to enforce the laws, and it has the authority to go on to farms to take any action necessary. However, he said, FDA and USDA prefer to use education to help producers comply with rules aimed at ensuring safe food. He pointed out that Federal Agencies are willing to cooperate with producers to develop the most workable programs, and he cited an egg safety program as an example

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FDA Veterinarian

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of the open development of policies the Federal Government uses.

Dr. Sundlof also cited the long-standing dairy program as a successful example of an industry-State-Federal program. And he cited the Federal program to prevent the establishment and spread of bovine spongiform encephalopathy (BSE) in the U.S. cattle herd as an example of a successful education program.

The reason for the Government's interest in food safety, Dr. Sundlof explained is in part because, while the U.S. food supply is one of the safest in the world, millions of people still get sick, and hundreds die each year from foodborne illness. In addition, scientists are learning more about food safety all the time. For instance, "we know of more than five times as many foodborne pathogens than we did in 1942," he said. Scientists and regulators have also discovered problems where none were expected, such as BSE, or salmonella transmitted via ovarian transfer to intact chicken eggs.

Three factors guide the Government's work in developing food safety policies, Dr. Sundlof said.

One, decisions must be based on science, and that means keeping Government scientists up to date on the most recent scientific developments. Over the past four years, the Government has doubled its investment in food safety, he said.

Two, decisions must also be risk-based. Government policies must address the real risks. And to discover what those real risks are, the Government will use risk assessments, he said.

Three, the Government will use open and transparent processes to develop food safety rules, he said.

Also on the first-day's program was Dr. Beth Lautner of the National Pork Producers Council (NPPC), representing the livestock producer's point of view, and Caroline Smith DeWaal of the Center for Science in the Public Interest (CSPI), representing consumers.

Later in the program, speakers included Dr. Catherine Woteki, Under Secretary for Food Safety for USDA, and Thomas Billy, Administrator of the Food Safety and Inspection Service of USDA.

Dr. Lautner, who is NPPC's Vice President for Science and Technology, said that producers have already taken the initiative to boost the safety of the food produced from the animals that come from their farms. Several producer groups already have industry quality assurance programs in place, she said, including pork, beef, sheep, dairy, veal, turkey, egg, fish, and others. Pork producers have also taken steps to address difficult issues, such as antimicrobial resistance. The group has developed educational material for producers that describes the prudent use of antimicrobials. Several other safety issues are also being addressed, she added.

CSPI's Ms. DeWaal presented the consumer point of view. The need to control foodborne pathogens as early as possible in the food chain "is critical to reducing foodborne illness in humans," she said. Ms. DeWaal is CSPI's Director of Food Safety. She said it has been shown that producers can take steps that are effective. "On-farm control programs for *Salmonella enteritidis* in eggs have proved successful in reducing both Salmonella contamination rates in shell eggs in the Northeastern U.S. and also reducing human illnesses linked to Salmonella enteritidis," she said. She cited new technologies that show promise in reducing pathogens in food, and said the European Union has demonstrated successful on-farm control methods. What would help speed implementation of on-farm pathogen control systems is the use of incentive-based regulations, Ms. DeWaal said. "Government action is needed to give farmers the incentive to develop and use technological solutions to food safety problems that originate on the farm," she said.

Dr. Woteki remarked that the nationwide implementation of the "Hazard Analysis and Critical Control Point (HACCP)" system was a "major achievement" for FSIS and the livestock slaughter industry. "HACCP implementation has gone very smoothly and has accomplished dramatic reductions in *Salmonella* in meat and poultry products," she said.

USDA is working on the principle that food safety is a farm-to-table process, which says that practices taken on the farm can have an effect on the safety of the food produced from animals, according to Dr. Woteki. For the future, she said, the U.S. Government and industry face four challenges.

One, continue progress in research and risk assessment "along the entire farm-to-table chain." On farm, "we need to identify cost-effective practices" that lead to reductions in food safety hazards.

Two, "we must recognize the links between the segments of the farm-to-table chain" so that all parts understand the interdependency of the food production system.

Three, the animal production industry should work on levels beyond their immediate concern. "For example, I encourage industry representatives at all levels of the farm-to-table chain to participate in the activities of the Codex Alimentarius Commission."

Four, industry and government should strengthen their partnerships to produce safer food.

Dr. Woteki said that the industry and Government together had already made considerable progress.

FSIS Administrator Mr. Billy also emphasized the farm-to-table approach to food safety. While HACCP has been implemented at slaughterhouses, livestock producers also have been developing complementary programs. "FSIS believes HACCP-compatible practices at the animal production level include producer recordkeeping, good hygiene, herd health management, residue avoidance and, where appropriate, pathogen reduction strategies," Mr. Billy said. Key food safety issues in animal production, Mr. Billy said, are

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FDA AND USDA SPONSOR FOOD SAFETY MEETING (Continued)

antibiotic resistance, residues (including microbial, chemical, or physical), and animal feed.

Mr. Billy, who is Chairman of the Codex Alimentarius Commission, said that food safety concerns are also important on the international front. "Through the Codex Alimentarius Commission, countries are working together to establish international consensus on food standards." In many cases, food safety standards have become central to international trade negotiations, he added. One principle the U.S. will always insist on, for both domestic and international work, is that food safety rules must be science-based, Mr. Billy emphasized.

During the second day of the program, there were two sets of breakout sessions. For the first one, the participants addressed specific issues, such as third-party verification of quality assurance programs. For the second session, breakout groups were organized around different species – beef and veal; dairy; pork; broilers and turkeys; sheep; eggs; and exotic and minor species. A designated individual from each of the breakout groups made a report at the end of the day to all of the meeting's participants, and those reports will become part of the proceedings.

Sponsors of the "National Conference on Animal Production and Food Safety" were:

- The U.S. Department of Agriculture
- Agricultural Marketing Service
- Animal and Plant Health Inspection Service
- Agricultural Research Service
- Cooperative State Research, Education, and Extension Service
- Food Safety and Inspection Service
- U.S. Department of Public Health and Human Services
- Food and Drug Administration
- Center for Food Safety and Applied Nutrition
- Center for Veterinary Medicine
- Professional and Industry Organizations
- American Association of Feed Control Officials
- American Association of Veterinary Medical Colleges
- American Farm Bureau Federation
- American Feed Industry Association
- American Meat Institute
- American Sheep Industry
- American Veal Industry
- American Veterinary Medical Association
- Animal Health Institute
- Center for Science in the Public Interest
- Federation of Animal Science Societies
- Holstein Association
- Livestock Marketing Association
- National Association of Federal Veterinarians
- National Cattlemen's Beef Association
- National Chicken Council
- National Institute for Animal Agriculture
- National Milk Producers Federation
- National Pork Producers Council
- National Renderers Association
- National Turkey Federation
- North American Elk Breeders Association
- United Egg Producers
- United States Animal Health Association

Jon Scheid is the Director of the Communications Staff in CVM's Office of Management and Communications. □

FDA RESCHEDULES MEETING

FDA's Center for Veterinary Medicine (CVM) public meeting to discuss the Establishment of Resistance and Monitoring Thresholds in Food-Producing Animals, originally scheduled for October 10-11, 2000, has been rescheduled. The new dates for the meeting are January 23 and 24, 2001. The meeting will be held from 8:30 a.m. to 5:00 p.m. at the DoubleTree Hotel, 1750 Rockville Pike, Rockville, MD, 20852. The meeting will discuss the Center's current thinking on the establishment of resistance and monitoring thresholds in food-producing animals. CVM will seek scientific input from experts at the meeting on these issues as well as suggestions for alternative approaches.

Registration for this meeting is free and is required. Limited space is available, and early registration is encouraged. If you registered for the October 10 and 11, 2000, meeting, you must re-register to attend the January 23 and 24, 2001, meeting. Logistics for the meeting as well as the registration form are available on the CVM Home Page at *http://www.fda.gov/cvm/fda/mappgs/ARThres.htm*. Information about the meeting is also contained in the September 26, 2000, *Federal Register* (*http://www.fda.gov/OHRMS/DOCKETS/98fr/092600b.htm*.)

For general inquiries about the meeting and registration, please contact: Lynda W. Cowatch, CVM (HFV-100), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-5281. Technical inquiries should be directed to Aleta Sindelar, CVM (HFV-6), at 301-827-4515. When making reservations with the DoubleTree Hotel (1-800-222-8733), please refer to the "CVM Antimicrobial Resistance Public Meetings" to receive the group discount rate. If you need special accommodations for a

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FDA's REGULATION OF HERBS & BOTANICALS INTENDED FOR USE IN ANIMAL DIETS

by John Machado, D.V.M., Ph.D. and Sharon Benz, Ph.D., P.A.S.

This information is adapted from a speech presented at the Symposium on Herbs and Botanicals in Livestock Diets:Current Trends, Efficacy, and Safety, from the ADSA-ASAS Joint Annual Meeting, held July 25, 2000, in Baltimore, Maryland.

Background

The use of herbal products is widespread and growing. The actual and perceived relative safety of natural products is a major reason for their popularity with the general public. In 1997, sixty million Americans spent 3.25 billion dollars on herbs as medical therapy. In 1999, United States herbal sales were expected to exceed five billion dollars. Unfortunately, the explosion in sales of such "supplements," has brought products to the marketplace that do not conform to the standards of safety and efficacy that we expect.

To better understand the concerns FDA has regarding the use of botanical and herbal substances in animal feeds, it is important to understand how these products are regulated.

FDA carries out the responsibility of regulation of animal feed products in cooperation with State and local partners through a variety of mechanisms: cooperative agreements, contracts, grants, memoranda of understanding and partnerships. For instance, FDA cooperates with the Association of American Feed Control Officials (AAFCO) and the States for the implementation of uniform policies for regulating the use of animal feed products. AAFCO helps to harmonize feed laws and regulations in the U.S. by establishment of model law and regulations, uniform feed ingredient definitions, and proper labeling rules to assure the safe use of animal feed products.

Federal Food, Drug, and Cosmetic Act

The use of food products is governed by the provisions of the Federal Food, Drug, and Cosmetic Act (the Act), and the regulations issued under it. The Act sets forth requirements for food products in the Sections 402 and 403. The Act requires that animal feeds, like human foods, be pure and wholesome, contain no harmful substances, and be truthfully labeled. Failure to meet these requirements can result in a product being deemed adulterated or misbranded. Adulteration includes, among other things, food packaged or held under unsanitary conditions, food or ingredients that are filthy or decomposed, food that contains any poisonous or deleterious substance, and food that contains unapproved food additives.

Dietary Supplement Health and Education Act

For decades, the FDA regulated "dietary supplements" as foods, to ensure that they were safe and wholesome, and that their labeling was truthful and not misleading. However, with passage of the Dietary Supplement Health and Education Act (DSHEA) of 1994, Congress amended the Act to include several provisions that apply only to dietary supplements. As a result of these provisions, dietary ingredients used in dietary supplements are no longer subject to the premarket safety evaluations required of other "new" food ingredients or for "new uses" of old food ingredients. Through the DSHEA, Congress expanded the meaning of the term "dietary supplements" beyond essential nutrients to include such substances as ginseng, garlic, fish oils, psyllium, enzymes, and mixtures of these. In addition, the DSHEA permits certain limited claims to be made about dietary supplements without resulting in the supplement becoming a drug.

Definition of Dietary Supplement

The DSHEA established a formal definition of "dietary supplement" using several criteria. A dietary supplement is:

- a product (other than tobacco) that is intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total daily intake, or a concentrate, metabolite, constituent, extract, or combinations of these ingredients.
- intended for ingestion in pill, capsule, tablet, or liquid form.
- not represented for use as a conventional food or as the sole item of a meal or diet.
- labeled as a "dietary supplement."

Inapplicability of DSHEA to Animal Products

On April 22, 1996, CVM published a notice in the *Federal Register* outlining why Congress did not intend DSHEA to apply to products for use in animals. Particularly, it was noted that under the food additive

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FDA RESCHEDULES MEETING (Continued)

disability, please contact the DoubleTree Hotel at least 7 days in advance.

Written comments about the meeting should be submitted by March 24, 2001. Comments should be directed to Docket #98D-0969 and submitted to: Dockets Management Branch, (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD, 20852; or faxed to (301) 827-6870 with the appropriate identification number. Questions about your submission of comments may be directed to HFA-305 at (301) 827-6860. □

provisions of the Act, FDA must determine that the product will not leave harmful residues in food before FDA can approve a product for use in a food-producing animal. However, nowhere in its revision of the regulation of ingredients in dietary supplements does the DSHEA address how the effect of supplements on food-producing animals and human food safety is to be assessed. Not only are there human food safety concerns, but when compared with human use of supplements, there is less information on the safe use of dietary supplements in animals.

In addition, many substances that fall under the definition of dietary supplements for human consumption, such as herbs and other botanicals, have a history of use in humans that can be used to establish reasonably safe levels. However, the same is not true for use of many of these same ingredients in animals. Moreover, each animal species requires different nutrients, absorbs and metabolizes nutrients differently, and can exhibit different toxic reactions to food and its components. The toxic reaction of dogs to chocolate is one example of species differences. The lack of information on the safe use of these kinds of substances in animals, and the fact that the animal population is not as homogenous as the human population are two more reasons why FDA has determined that the DSHEA should not apply to animal products.

Finally, many drugs intended to increase the production of meat, milk, egg, or fiber (so called production drugs) or otherwise affect animal performance could arguably be covered as dietary supplements under the DSHEA. Currently, products bearing such production claims are animal drugs under the Act, and as such, can only be marketed after approval by FDA after the manufacturer conducts extensive scientific studies to show that the drug is both safe (in animals and humans) and effective.

In summary, there are significant complex scientific and regulatory issues relating to human and animal safety that would need to be resolved by Congress before a similar scheme for animal supplements could be put in place. Accordingly, FDA has concluded that animal dietary supplements are not covered by the DSHEA.

It is important to note that DSHEA defines the term "dietary supplement" to exclude products intended for use as conventional foods. For example, St. John's Wort would not be considered a dietary supplement if it were added to soup. Soup is a conventional food and any ingredient added to conventional foods must be used in accordance with its food additive regulation or be generally recognized as safe (GRAS) for its use in soup.

Market Availability

Nevertheless, many dietary supplements are being marketed for use in animal diets. Many of these products contain botanical and herbal ingredients. While the majority of these are intended for companion animals such as dogs, cats, and horses, there are products that are intended for food-producing animals. These products are often promoted as nutraceuticals, and may contain a number of herbal substances (see Table 1). Currently, none of these ingredients is accepted for use in animal feed.

Safety Concerns

Most of these herbal products contain substances possessing significant pharmacological activity and consequently potential adverse effects. The specific ingredients that determine the pharmacologic activity of the product are generally unknown.

California investigators in 1998 found that nearly one-third of 260 imported Asian herbal remedies were either spiked with drugs not listed on the label or contained potentially hazardous levels of lead, arsenic or mercury. The potential for diversion of such hazardous products or their by-products, for use in food-producing animals is a matter of serious safety concern.

Use of herbal products in lieu of veterinary care is also a concern. For example, in one country, comfrey is purported as a drench for swine to treat "fevers." It also is recommended as a treatment for dogs after hip dysplasia surgery. Some other oral uses of comfrey in dogs include treating rickets, arthritis, and rheumatism. For livestock, it is recommended as a treatment for ulcers, arthritis, and rheumatism. In the U.S., comfrey has been marketed in horse products as an anti-inflammatory and to promote wound healing. No published studies could be found to support these medicinal claims.

Moreover, there are several dangers associated with the use of comfrey.[1] Comfrey contains at least eight pyrrolizidine alkaloids (PA). PAs are hepatoxins and can cause irreversible liver damage. Since the alkaloid effects are cumulative, it may be difficult to associate the damage to the liver with alkaloids in comfrey. Sometimes toxicity signs will not be present until an animal is stressed by something that requires greater liver function (e.g., lactation). Also, the leaves and roots of comfrey have been shown to be carcinogenic. PAs from comfrey given to rats caused mortality. Liver pathology was characteristic of PA toxicosis. When rats were fed dietary levels of 0.5% roots and 8% leaves, they formed hepatomas.

Another concern of comfrey feeding would be the safety to humans consuming meat and milk. One study has shown that small amounts, (less than 0.5%) of PA can be transferred to the milk (Dickenson, 1976, JAVMA 169:1192). However, there appears to be no research regarding residue in meat. There are questions that need to be answered: what happens to PAs when animals consume them, how

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are they metabolized, and are PAs and their metabolites transferred to meat, milk, and eggs.

Generally Recognized as Safe Herbs

In the absence of drug claims, the use of herbal substances in animal feeds is regarded as a food use. This regulatory status determination is made by CVM on a case-by-case basis. Botanical ingredients allowed in animal feeds, considered GRAS, are listed as flavoring agents under Part 582, Title 21 of the CFR. These include common herbs such as oregano, thyme, rosemary, etc. These are acceptable for use in animal feeds as flavorings and the level of use should be in accordance with their use as a flavoring. Most flavorings are used in part-per-million levels.

Product Claims

With regard to claims, we emphasize that an animal food label must not state and/or imply that the introduction of the product in the animal's body results in a physiological or therapeutic effect. Under the Act, claims in or on animal feed products that establish the intended use to cure, treat, prevent or mitigate disease, identify the intent to offer the product as a "drug." For example, statements on promotional material associating the use of the product with prevention or treatment of diseases such as *E.Coli* and *Salmonella* infections could establish the use of the product as a drug. If the promotional material is documented as labeling, these statements are enough to establish the intended use of the product as a new animal drug. Unless the product has been shown to be safe and effective for its intended use via approval of a New Animal Drug Application, it could be subject to regulatory action as an adulterated drug.

In addition, claims that establish the intended use or affect the structure/function of the body in a manner other than food (nutrition, aroma, or taste), identify the intent to offer the product as a "drug." However, statements associating the nutrients in the product with their "known" functions may be acceptable provided they are truthful and not otherwise misleading. On a case-by-case basis, CVM has allowed references to "nutritional support" for specific organs or body functions. For example, we would not object to a claim that an animal food product contains vitamin E for prevention of fat oxidation in the feed or serves as an antioxidant in the body.

Interaction with AAFCO

To the current market situation, FDA and AAFCO are currently working to establish procedures to evaluate the use of "novel" ingredients in animal foods. In 1999, the AAFCO's Novel Ingredient Task Force was formed and charged to set forth a regulatory scheme for these novel ingredients. Botanicals and herbs are part of a group of substances recognized by AAFCO as "novel ingredients." The Novel Ingredient Task Force recommends that a standing committee be formed to specifically address botanical and herbal ingredients.

The Botanical and Herbs Committee met for the first time at the AAFCO's Midyear meeting in Phoenix, AZ, in January 25, 2000, and again in July 2000 in Charleston, WV. The committee decided that a survey would be taken of the animal feed industry to determine which ingredients are currently on the market or

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Table 1.

Some unapproved herbs currently marketed for use in animals. The herbal plant common name is followed by its scientific name, in parenthesis. It is noted that most of these plants are also known by other common and scientific names.

Herb	*Claims*
Arnica (*Arnica spp.*)	Anti-inflammatory and stimulant
Boneset (*Eupatorium perfoliatum*)	Vasodilator and antispasmodic
Burdock (*Arctium spp.*)	Digestive aid, improve liver and kidney function
Clivers (Galium aparine)	Diuretic, treatment of urinary problems
Comfrey (*Symphytum officinale*)	Anti-inflammatory, promote wound healing
Devil's Claw (*Harpagophytum procumbens)*	Anti-inflammatory, alternative to Bute
Echinacea (*Echinacea angustifolia*)	Improve function of the immune system
Ginseng (*Panax ginseng*)	Enhance immune system, promote lung function
Horsetail (*Equisetum arvense*)	Promote healing of connective tissue and acts as a diuretic
Ignatia amara	Sedative
Nettles (*Urtica dioica*)	Diuretic, treat anemia
Uva-Ursi (*Arctostaphylos uva-ursi*)	Diuretic, urinary antiseptic
Valerian (*Valeriana officinalis*)	Sedative
White willow bark (*genus Salix*)	Arthritis, anti-inflammatory
Yucca (*Yucca schidigera)*	Arthritis

utilized by animal health care professionals. The results of the survey revealed that there are about 180 botanical species currently being marketed or used by animal health care professionals in the United States.

Summary

The FDA is charged with enforcement of the Act which requires that animal foods be pure and wholesome, contain no harmful or deleterious substances, and be truthfully labeled. Although not covered by DSHEA, currently many dietary supplements, including herbal supplements, are being marketed for use in animal diets. Since most herbal products contain substances possessing significant pharmacological activity and consequently potential adverse effects including harmful residues, the use of these products in food-producing animals is a major safety concern.

Dr. Machado and Dr. Benz are members of CVM's Nutrition & Labeling Team in the Division of Animal Feeds.

[1] Taken from the Cornell University's Home Page on the Internet at: http://www.ansci.cornell.edu/plants/medicinal/index.html.

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CHORULON®: A CASE STUDY OF FLEXIBILITY IN THE NEW ANIMAL DRUG APPROVAL PROCESS

by Kevin J. Greenlees, Ph.D., DABT

Introduction

CVM began a new era in the regulation of new animal drugs and feed in aquaculture in the early 1990s. This era began with a recognition of the need for education in the area of aquaculture and new animal drug requirements and led to an intensive educational effort on the part of both CVM and the aquaculture industry. A concerted effort followed to create investigational new animal drug files and to develop data for the approval of new animal drugs for aquaculture. The Joint Subcommittee for Aquaculture – Working Group for Quality Assurance in Aquaculture Production was established with co-leadership provided by CVM and USDA.

The aquaculture industry's need for pharmaceutical tools to facilitate the production of a high quality agricultural food product, coupled with the paucity of approved new animal drugs in aquaculture, led to an early focus on development and appropriate use of new animal drugs. Various efforts were made by CVM to educate the aquaculture industry on the requirements of the Federal Food, Drug, and Cosmetic Act, and numerous aquaculture experts came to CVM to educate the regulatory scientists and others in CVM on the needs and practices of the industry.

This effort continues, and is most clearly demonstrated by the existence, with continued financial support by CVM, of the National Coordinator for Aquaculture New Animal Drug Applications, Ms. Rosalie Schnick, and a dramatic expansion in the number of scientists dedicated to aquaculture at CVM. Despite this intense effort, and despite the efforts of the pharmaceutical industry, development of approved new animal drugs for aquaculture has been very slow. The successes include a generic drug approval expanding the choice of sources for the approved drug tricaine methanesulfonate.

Supplemental new animal drug approvals have expanded the claims for formalin to all finfish for control of protozoa and monogenic trematodes, and all finfish eggs for control of fungi of the family Saprolegniaceae. The many challenges facing approval of new animal drugs for use in aquaculture will not be discussed here. The subject of this brief article is the recent approval of Intervet, Inc.'s Chorulon® (chorionic gonadotropin) as a spawning aid for brood fish, and the flexibility of the approval process.

Discussion

Chorionic gonadotropin (human chorionic gonadotropin and pregnant mare serum gonadotropin) has been approved for some time for use in cows for treatment of nymphomania (frequent or constant heat) due to cystic ovaries, using a single intramuscular injection. The Chorulon® supplemental approval (for the use of up to three intramuscular injections of Chorulon® as a spawning aid for male and female brood fish) provided CVM with the opportunity to implement a number of initiatives that have been proposed over the years to facilitate the use and approval of new animal drugs. This began even during the development of the new animal drug for its intended use in brood fish.

Because chorionic gonadotropin's potential extra-label uses are not as a therapeutic drug to treat or control disease, it cannot be used extra-labelly under the provisions of the Animal Medicinal Drug Use Clarification Act (AMDUCA). It was recognized that chorionic gonadotropin was a critical tool for much of the aquaculture industry for the maintenance and development of fish stocks. As such, CVM took the unprecedented step of publishing a guidance permitting the use of the unapproved new animal drug in brood fish under certain conditions (Guidance for Industry #71). This action provided the use of the unapproved new animal drug, chorionic gonadotropin, under regulatory discretion. The decision to provide this discretion was based on the low human food safety and environmental safety, the need of the industry for

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this relief, the food fish status of many of the broodstock which would receive treatment, and the likelihood of a formal approval for this use. CVM also took into account the life-stage of the fish being treated (Guide 1240.4260) and the regulatory priority for enforcement of this drug use (Guide 1240.4200). Following the approval of Chorulon®, the guidance was rescinded, and the aquaculture industry was reminded to use the approved new animal drug, Chorulon®.

CVM's flexibility facilitating availability of the unapproved new animal drug was a step in maintaining the partnership between CVM, the aquaculture industry, and the pharmaceutical sponsor. Further evidence of flexibility on the part of CVM is clearly evident in the Chorulon® freedom of information (FOI) summary (FOI NADA Number 140-927). For example, in 1998, CVM published a guidance on the use of professional flexible labeling for antimicrobial drugs (Guidance for Industry #66). The concepts contained in this guidance for antimicrobial drugs were applied to the production use of Chorulon® (a hormone with no antimicrobial activity) for spawning. There is, in fact, no single dose recommended for the safe and effective use of Chorulon®. Various dose ranges are presented for specific finfish species. This leads to the other key component of the Chorulon® approval: crop grouping.

Crop grouping refers to the grouping of species so that one or more representative species may be chosen for use in safety and/or effectiveness studies for a new animal drug approval. For example, rainbow trout or Atlantic salmon can be used to represent all salmonid species, and data for the approval of drugs for use in dairy cattle are typically generated in Holstein cattle, the predominant dairy breed in the U.S. Crop grouping concepts as understood by CVM have been presented to the aquaculture industry as part of the general guidance on drugs for minor use and for minor species (Guidance for Industry #61). What is unique about crop grouping in aquaculture is the need to extend the grouping not just to other breeds, but to other species and even other genera as well.

Safety and effectiveness of Chorulon® are presented in the FOI summary. Based on the results of pivotal effectiveness data in 8 species, pivotal target animal safety data in 4 species, and supporting data in numerous species of finfish, CVM was able to determine that Chorulon® would be safe (to the animal) and effective (as an aid in spawning) in all finfish broodstock. This is an example of the impact of crop grouping – the more traditional approach would be to limit the approval to those finfish broodstock species for which there was acceptable pivotal data. The indications for the approved use of Chorulon® are:

CHORULON® should be administered, depending on the fish species, at a dose of 50 to 510 I.U. per pound body weight (BW) for males and 67 to 1816 I.U. per pound BW for females, for one to three injections. Table 3.1 contains the recommended dosages for several representative fish species. The dose of CHORULON® to be used in other species of finfish may differ from those listed in the table, but should fall within the suggested range of 50 to 510 I.U. per pound BW for males and 67 to 1816 I.U. per pound BW for females.

Another unique aspect of this approval may be found in the FOI summary. The data demonstrating the safety of Chorulon® to the animal, and effectiveness of the proposed use, was generated by a number of independent investigators under various investigational new animal drug files (INADs), as well as by the sponsor of the new animal drug (Intervet). This successful cooperative pooling of resources between the aquaculture industry and the pharmaceutical sponsor was a key factor in the generation of data supporting the approval of the new animal drug application.

The human food safety considerations for the approval of Chorulon® are well documented in the FOI summary. When chorionic gonadotropin was approved for use in cows, the safety was based upon the use of the product and industry practices, and an assumption that oral gonadotropins would not be orally bioavailable. Because of the different conditions of use in aquaculture, and the much higher proposed dose, there was a need to address the safety of total chorionic gonadotropin in the diet. The approach taken, as described in the FOI summary, was to require data to show the relative oral bioavailability of chorionic gonadotropin in a sensitive animal model. It was shown that oral gonadotropins were without effect unless administered at a very high dose. In addition, it was recognized that the worst case dietary exposure to Chorulon® would be the potential consumption of the tissue into which the drug had been injected (the injection site) without allowing any time for the drug to deplete. Even in this unlikely event, it was determined that as much as 25,350 I.U. of total gonadotropin would be safe for a person to consume.

It was clear from the effectiveness data that in nearly all instances the total amount of Chorulon® administered to the fish would not be sufficient to cause concern in the human diet. In addition, consideration of the life-stage for which the drug is intended (broodstock), and the purpose (spawning) provided assurance that it would be very unlikely for the drug to be used for other applications, and that the numbers of fish requiring such a high dose would be very small. As a result, the human food safety for Chorulon® could be established in all finfish, with the following unique limitation:

No withdrawal period is required for brood fish treated according to

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label directions. The total dose administered (all injections combined) should not exceed 25,000 I.U. HCG (25 mL) per fish in fish intended for human consumption.

Conclusion

The approval of Chorulon® has opened the door to innovative approaches in new animal drug approvals. While maintaining high standards for safety and effectiveness, it offers an example of flexibility and innovation in meeting requirements to approve a new animal drug. Only time will tell whether these approaches will have a significant impact on future approval of new animal drugs for aquaculture or other purposes.

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DAIRY SAFETY TRAINING IN EL SALVADOR

FDA in collaboration with USDA's Foreign Agricultural Service (FAS) hosted a Central Region Dairy Safety Training Course ("Focusing on On-Farm Dairy Practices") in San Salvador, El Salvador, August 7-11. A total of 60 participants attended from government, industry and academia. They represented Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Panama, and Nicaragua. These nations provided the materials and instructors for the course. FDA worked closely with representatives of the U.S. embassies in El Salvador and Guatemala who provided the support staff and local arrangements.

Course topics included: sanitation and animal health on the dairy farm, proper use of medication and waste removal, prevention of drug residues, construction of dairy farm facilities and milking practices for safe milk, safe water supplies, milking facilities and cooling equipment, control of rodents and insects, proper methods of sampling milk on the farm, cooling and transporting milk, inspection methods, and record keeping. There was also a series of presentations by attendees of the dairy industry from the respective countries. They discussed the unique challenges presented by the tropical climate and how dairy safety practices are applied in each country. Evaluations of the course were very complimentary and 58 of 60 attendees rated the course a great success. Attendees expressed need for a similar course on milk safety in the processing plant.

The U.S. training cadre consisted of Heinz Wilms [Food Safety Initiative (FSI)], Capt. Richard Eubanks [Office of Regulatory Affairs/Division of Human Resource Development (ORA/DHRD)], Mike Davis (ORA/SW Region), Mike Talley (CVM), Frank Flores (TX Dept. of Health). Dr. Oscar Bruni, President of the National Service of Agro-alimentary Health and Quality in Argentina (SENASA) visited CFSAN to meet and discuss issues on FSI, Seafood HACCP and Dairy. Dr. Bruni expressed an interest in hosting a regional road show and collaborative exchange with government officials. FDA representatives were Walter Batts, Lois Beaver and Luis Solorzano [Office of Internal Affairs (OIA)], Marion Allen (FSI), Robert Childers [Office of Field Programs (OFP)], Tim Hansen and Ellen Nesheim [Office of Science (OS)].

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by Cindy Burnsteel, D.V.M.

Dr. Cindy Burnsteel is a Veterinary Medical Officer in CVM's Division of Therapeutic Drugs for Food Animals, Office of New Animal Drug Evaluation. She continues to practice large animal medicine, and recently traveled to Honduras to share her medical expertise. This is an account of her experience while on a two-week leave from FDA.

The veterinary profession offers a myriad of opportunities to those who wish to "care for animals." While the majority of veterinarians are employed in private practice, the possibilities for service are endless. As a large animal practitioner, I have spent eight years taking care of cattle, sheep, goats, pigs, and horses in the eastern United States. In June of 1998, I was presented with the opportunity to travel abroad to provide veterinary services in Honduras, Central America.

In June of 1998 and 1999, I traveled with a group of medical professionals to Honduras, under the auspices of Medical Ministries International. During the 1999 trip, I was able to provide veterinary services to approximately 2,030 cows and calves, 160 horses, 100 dogs, 60 pigs, 50 sheep, and some rabbits. The dental clinic saw 2,384 patients and pulled 2,895 teeth. One thousand thirty-five children received fluoride treatments and their own toothbrush and toothpaste. The physicians provided medical care for approximately 3,000 people. Over 8,000 prescriptions were filled and 20 people received physical therapy within their homes. A local school was repaired and reinforced by our construction team. All of this took place in eight working days.

In June of 1998, I joined a team of approximately 90 other Americans en route to Honduras. The majority of the team (teenagers included) would serve as "general helpers", just ordinary people with a desire to give of themselves for others less fortunate. The rest of the team consisted of pediatricians, general practitioners (M.D.'s), dentists, dental hygienists, oral surgeons, physical therapists, nurses, and two pharmacists. I would be the only veterinarian on this trip. In preparation for my trip, I contacted

the veterinarian who had traveled to this same village the year before. He is a small animal practitioner, who did a lot of large animal work while he was in Honduras. This news excited me, because I wanted to do mainly large animal work! We spent many hours on the telephone sharing information. I remember vividly that while talking with me, he kept saying, "I wish that I was going back." His experience was so positive that I could not help but be anxious for the trip to start. It was exciting to have the opportunity to help people who relied so heavily on their animals for their livelihood.

From June 12-26, 1998, the town of Trinidad, Santa Barbara, Honduras was home. The country is beautiful and the people could not have been nicer, nor more appreciative of our help. Our accommodations were rustic, we slept on cots on the floor, took cold showers, and ate lots of rice and beans, and yet we all came back better people than we had been before we left. The stories are endless, from working on a farm high above the clouds, to horseback riding through a coffee and banana plantation. There were special days when something happens that make you know that you are there for a reason. One such day, we were working high up in the mountains, and as we were driving down, we passed a man walking with an older woman. Our driver seemed to know everyone, and we often stopped to give people a ride. As the old woman helped the man into the bed of the pickup, we saw that the man had a very bad cut across the top of his hand. Apparently this was a very common injury. He had cut his hand with a machete while working in the fields. This injury usually resulted in the loss of function to the hand, because of the lack of medical care available. We took him back to our medical clinic, where he spent the following 2 ½ hours in "Oral Surgery" having his tendons sutured back together with my 'cow suture' (the surgeons had

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not planned on needing suture that strong). He came daily for wound cleaning and antibiotic injections. When it was time for us to leave, arrangements were made for him to go to the city (a 2-hour trip by bus), for medical attention. The hand was looking good and we were all very hopeful that he would regain full use of his fingers. I spent my last day in a "question and answer" session with all of the farmers that belonged to the co-op. We were able to provide the farmers with information about animals and crops.

After returning home, I naturally reflected on all that we have and the many people that have so little. I knew I would return again; every-other-year was my plan. As June of 1999 approached, several of my friends were getting ready for the Honduras Trip. Another veterinarian was planning on going, and I spent one evening talking to him on the phone. He expressed his concern that in only two weeks, he surely could not make a difference. This concern is raised by a lot of people, but I assured him that everything that he did in those two weeks would make a difference, to the people, as well as the animals. Those 2 weeks of veterinary care, might be the only medical attention that those animals would ever receive. Anything is better than nothing, I told him. By the end of our conversation, he had decided that he would go, and I was wishing that he wouldn't, so that I could go in his place. As it turned out, he had a previous commitment that could not be changed. With only 6 weeks remaining until the trip, I was called and asked if I could serve. Although I had not planned on it, I felt compelled to go. There were many arrangements that needed to be made. I had since changed jobs and needed to see if time-off could be arranged. FDA graciously allowed me to take my 2 weeks leave at one time on very short notice. Then there was child-care and pet care arrangements to be made. Everything seemed to fall into place and I began gathering supplies and medications to take with me. Medications, both human and animal alike, are carried with us in our luggage; one suitcase for medicine and the other for personal items. I was able to use one other person's suitcase, as well as my own, for the transportation of veterinary supplies. This past year I had acquired more medications than I was able to carry. I contacted several shippers and was delighted when FedEx responded that they could ship 100 pounds of products free of charge. The boxes were shipped on a Tuesday night, and were waiting for me at the airport when I arrived in San Pedro Sula that Saturday.

The "team" gathered at the airport in Honduras, with old friends getting reacquainted, and new friendships being forged. We were met by the Castro family, native Hondurans who coordinated this trip as well as many others throughout the year. Once the luggage was loaded in the truck, and the people loaded into buses, we headed off to our destination. This year San Luis, Santa Barbara, Honduras, would be our home from June 10-24, 2000. It was 62 kilometers from the airport; a 4-hour ride by bus—made longer by mechanical difficulties. The first hour is on blacktop, then dirt roads. The country is still suffering from the aftermath of Hurricane Mitch that left many rivers and roads impassable.

We arrived in the middle of a bad storm, to flooded streets and no electricity, but dinner was laid out for us and we ate by light from gas lanterns. San Luis is a much larger city than Trinidad, with a population of 32,000. Not everyone lived in the town, half of the people live in the remote villages nestled in the mountains. We occupied two schools, one for living quarters and the other for the medical clinic. Each room was shared by about 15 people, cots on the floor with a chair for your suitcase. Showers were still just cold water, although the "seasoned MMI'ers" bring "hot showers", bags that heat the water from the reflection of the sun's rays. The city is high in the mountains so the nights were cool and the days warm (80-90°F), but comfortable.

The first night was spent getting settled into our rooms, by flashlight. The following day was consumed with setting up the medical/dental clinic, and counting out vitamins for distribution. Each morning began with an informal gathering on the bleachers, for announcements, a brief message and singing—both in Spanish and English. Breakfast was served at the theological school, 400 yards up the hill. The rest of the group then walked to the medical clinic, about 2 miles away. As the local people learned our schedule, many brought their vehicles to provide transportation for our people. The farmers quickly learned to pick me up at my room—where all of my veterinary supplies were stored in Rubbermaid® containers. The supplies were loaded onto the back of the truck, then it was up the hill to breakfast and then out for the day.

My first day was spent with Mark don Torro and Javier Matta, two well-respected farmers of the community. We developed a quick friendship and most days one of them accompanied me. That evening, I put on a question and answer seminar for the farmers. I had expressed to our coordinators that I thought this should occur at the beginning and not at the end of our visit. I was very fortunate that an American missionary couple were in town visiting friends. Keith Ackerman served as my interpreter for the evening. All of the farmers knew him and they were very receptive to what I had to say. A schedule was established that first night, and each morning I was met by the farmers whose animals I would be treating that day. The farmers all worked

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together, and it was not uncommon to have several pick-up trucks going with me. They were all eager to learn as much as they could, by watching me work and by talking to me. I took one or two teens from our group with me each day as general helpers and an interpreter. The interpreters were teens from the bilingual school in the city. Most had no knowledge of farming or cows, but the scenery and fresh coconut made it worthwhile. My Spanish continued to improve as I made every effort to communicate with the farmers. They were also eager to communicate and encouraged conversation.

Most of the work I did was to deworm cattle and vaccinate them against *Clostridial* disease. The cattle in San Luis are dual-purpose, they are raised for milk and for meat. Most are Brahman or Brahman crossed with Brown Swiss. There were very few Holsteins, as they are not very heat tolerant and they do not navigate the terrain very well. The cattle all have horns, very large horns. These are necessary because this is how they are caught, by a lasso over the horns. Very few farmers (only two) had a chute or any cattle working facility. Most farms had small corrals where the cattle were gathered. Work is done by roping the individual animal and tying her to a tree. The cattle are, suprisingly, very calm—nothing like the rodeo bulls that we are used to seeing here in the U.S. Their bulls are huge, but very quiet and gentle (and I don't like bulls!). The farmers were very good at watching out for me and keeping me out of harms way.

Each day was different from the last. One day we spent 4 hours vaccinating and de-worming 170 cows, with two brothers roping the cattle. We were in a beautiful valley between two mountain ranges. The country was mountainous and very green, this was the start of their rainy season. Crop farming is very different there than it is here in the U.S. Most crops are planted on the side of a mountain, by hand. The scarce flat land is used for growing the export crops of sugar cane, pineapples, and bananas. Most farmers also grow coffee and bananas together. The bananas are planted to provide the shade necessary for the coffee plants.

Another day we drove one hour to a farm, only to find out that the owner was up the mountain. Time definitely is not as important to these people as we perceive it to be. It was nice to be able to just sit and wait. We passed the time by coloring with Orlando, the five-year-old son of the driver. I had brought some coloring

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books and crayons to give to the children. Many of us, who return year after year, find room in our baggage to bring small toys, shoes, and clothing for the children. They seem to have so little and yet they always have a smile.

The day I remember most started the morning after a torrential storm. We had to drive across a river (no bridges, through the water) several times to reach our destination. (The river was very deep for driving.) After we crossed the river for the fourth time, we drove 100 yards up the hill and parked. I got out and looked for the cattle. There they were in a corral, on the opposite side of the river! Then I looked closer and saw only a narrow log connecting the two riverbanks. My first impression was that I was NOT walking across that log—a thought echoed by the teens with me that day. The farmer assured me that all would be fine and that he and his brother would carry all of the supplies. This was definitely one of those times when you didn't want to forget anything. They made several trips across like they were walking down a sidewalk. When it was my turn, I started across and then decided that I really couldn't do it. I wanted to get there the way the cows did, and, I knew that they didn't walk across this bridge. One of the brothers came back and helped me across (and back again also!). There were two more log bridges to cross that day, but they were more advanced. They had bamboo handrails, which weren't much, but it made all of the difference in the world!

Saturday was a half-day for the medical clinic, but I worked all day. I had lots of help and traveled to many farms, it was a very productive day. Most of the work was routine procedures for cattle, but I also stopped by a rabbit farm. I didn't have much experience with rabbits, but was able to answer the owner's questions and offer advice. (I have since located a rabbit manual in Spanish, and will send it down to him.) There was another log bridge to cross this day, but it was much wider *and* had a handrail! My interpreter for the day took a picture of me and the ten farmers on the bridge.

Sunday was a day of rest. The town hosted a picnic at one of Javier's farms and we ate lunch in a banana grove. I had brought ten containers of bubbles and the local children had a great time playing with them. That night there was a traditional dance presentation at the cultural center, and a local dance afterwards.

We worked Monday through Wednesday of the second week. The medical clinic is only open half a day on Wednesday, in order for everything

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to be packed up by the end of the afternoon. I stayed gone all day, working at the village of Las Flores. It took an hour to get there, and when we arrived, I remember thinking that there could not possibly be as many animals here as they had indicated. The road literally came to an end on a mountain plateau, bordered by three houses. There were five children playing, several horses grazing, and in a small corral, there were 11 cows and a bull. I got right to work with the animals, while my assistants handed out coloring books and crayons to the children. Hours later, when we left all 50 coloring books and sets of crayons had been handed out. Over 100 horses were dewormed; 50 dogs vaccinated against rabies, and treated for internal and external parasites; 30 pigs were dewormed; and four different 'herds' of cattle were vaccinated and de-wormed. On our way back to town, we stopped by several small farms that we had not yet visited, and provided veterinary services to their animals. By this time, supplies were getting short, but they were happy for what we did have.

Wednesday night was our farewell dinner/ceremony. Many of the people in town were present. The Castro family took turns interpreting for us while the mayor gave a speech of appreciation, and expressed the town's desire to have us return next year. Then the farmers got together and said thanks to me. What a great feeling it was to be recognized in that way. Gifts were exchanged and we were each presented with a small woodcarving and a book about the history of San Luis (in Spanish).

The following morning, many people came to say good-bye and to thank us again. As we drove through town, people were waving and calling out to us, and children ran along side of the buses. We headed to the city of San Pedro Sula for pizza from Pizza Hut®, and a day of tourism before heading back home. I chose the "Boat tour of Lake Yohoa and a trip to a waterfall". It was beautiful.

I already have plans to go back to San Luis again in June 2001. I have also contacted a local college in the country and hope to work with their agriculture department for a few days. One year, when my son is older, he will join me. I would encourage any of you to think about going on such a trip, if not this year, maybe the next. There is a job for everyone, no matter where your talents lie. You work hard, but you gain much more than you give.

My Spanish improved, and I made new friends. I learned how to rope cattle and how to take time to enjoy my surroundings. I learned that it is really not difficult to live without electricity for two weeks and that it is quite peaceful when the phone never rings. I learned that great joy can come from sitting on a porch talking to friends while the rain pours down. And, I know that I made a difference in the lives of the animals, and the people whose lives depend on them.

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CVM HOSTS VETERINARY FIELD COMMITTEE MEETING

by Barbara Rodgers

On September 13, 14, and 15, 2000, the Division of Compliance, Office of Surveillance and Compliance, hosted a FDA Veterinary Field Committee Meeting. Traditionally, this meeting is held only once a year, in December. However, at the request of Ballard Graham, FDA Atlanta District Director, this special meeting was convened.

The membership of this committee has changed radically in the last year. Starting at the top, Ballard Graham became the chair following the retirement of Mike Rogers, FDA Kansas City District Director, who had chaired the committee for five years. In addition, with the departure or reassignment of several other committee members, a new roster for the committee was established.

Members are as follows:

Diana Kolaitis, Regional Food and Drug Director, NE Region – Advisor

Ballard Graham, Atlanta District Director – Chair

Tom Gardine, Philadelphia District Director

Jim Rahto, Minneapolis District Director

Gayle Lancette, Director, SE Regional Laboratory

Ric Long, Director, Pacific Regional Laboratory NW

Darrell Lee, San Francisco District, Director, Compliance Branch

Jerry Woyshner, New York District, Director, Investigations Branch

Noel Ferguson, Kansas City District, Consumer Safety Officer

Following opening remarks by John Marzilli, Deputy Associate Commissioner for Regulatory Affairs, Office of Regulatory Affairs (ORA) and the introduction of John Taylor, the new Director of the Office of Enforcement, ORA, Linda Tollefson, Director, Office of Surveillance and Compliance (S&C), outlined the CVM priorities for FY 2001. These include antimicrobial resistance,

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new animal drug preapproval activities, MUMS (Minor Use – Minor Species), tissue residues, the adverse reporting system, and aquaculture monitoring.

The comprehensive agenda covered a variety of topics. Animal feed issues included updates on Bovine Spongiform Encephalopathy, the Voluntary Self Inspection Program, Veterinary Feed Directive Drugs, Dioxin, and Pig Ears and Pet Chews. This information was provided by CVM's Division of Animal Feeds and the Division of Compliance, S&C. A presentation on the Adverse Experience Reports Initiative and updates on the collection of promotional advertising for unapproved products and the records and reports regulations were given by the Division of Surveillance, S&C.

The Division of Compliance Structure/Function Subgroup presented their plan for the restructuring of the Division of Compliance. This restructuring will streamline the workflow in the Division and provide more timely completion of documents.

Other presentations given by CVM included: the transgenic fish issue, the aquaculture drug initiative, and a tissue residue update. ORA discussed the FY 2001 workplan, State contracts and partnerships, bulk counterfeit drugs, and training.

Ballard Graham encouraged CVM to participate in activities of the Association of Food and Drug Officials (AFDO) and similar local associations. He also pledged his support and that of the entire field committee in helping CVM to work effectively and efficiently with ORA field and headquarters units. Several action items came out of this meeting for future initiatives between CVM and ORA. The next meeting of the Veterinary Field Committee will be held in the spring of 2001.

Barbara Rodgers is a Consumer Safety Officer in CVM's Compliance Information Management Team in the Division of Compliance.

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CVM CONTINUES WORK ON METHODS TO DETECT PROHIBITED PROTEIN

by Burt Pritchett, D.V.M., and Dragan Momcilovic, D.V.M.

CVM sponsored a session at the International Workshop on Diagnostics of Transmissible Spongiform Encephalopathies (TSEs) devoted to its efforts to develop methods for detecting prohibited protein in animal feed. The workshop, sponsored by FDA and the National Institutes of Health (NIH), was held September 20 – 22, 2000, at the NIH campus in Bethesda, MD. CVM Director Dr. Stephen Sundlof opened the session, followed by remarks from session co-chairs Dr. Dan McChesney and Dr. Avraham Rasooly. Other sessions at the workshop focused on the latest developments in antemortem and postmortem diagnostic tests to detect TSEs in man and other animals.

In seeking diagnostic tools to enforce the mammalian-to-ruminant feed ban, CVM drew on the BSE experience of Europeans by inviting speakers from the United Kingdom (UK), Switzerland, and Italy to discuss their tests and other efforts to control the spread of TSEs through animal feed. Among many distinguished presenters, Dr. Mike Ansfield, Ministry of Agriculture Fisheries and Food, UK, talked about the challenges, both scientific and regulatory, in enforcing the UK feed ban, which is similar to the U.S. feed ban. Dr. Lucas Perler, Swiss Veterinary Authority, Switzerland, gave an overview of the BSE situation in Europe, with emphasis on the highly regarded and highly effective active surveillance program employed by the Swiss to detect BSE in their cattle population. France has already begun using a similar surveillance program and other European countries are considering adopting it. Dr. David Taylor, Sedecon 2000, UK, elaborated on safety of meat and

(Continued, next page)

bone meal. Dr. Christoph von Holst, European Union, Joint Research Center, Italy, specified the validation criteria for methods for detection of prohibited ingredients in feed.

Dr. Don Franco, National Renderers Association, elaborated on steps and measures that his association performs in order to maintain the safety of the U.S. meat and bone meal, while Dr. James Makowski presented feed microscopy as a means for detection of prohibited material. Dr. Mike Myers, CVM, talked about FDA's validation of a method that is based on use of polymerase chain reaction (PCR). Dr. Dragan Momcilovic, CVM, gave an overview on other methods for detection of prohibited materials in ruminant feed and elaborated on the potential for their improvement in the future.

Methods currently in use to detect proteins in feed are inadequate for reliably determining whether a sample of animal feed complies with the existing regulation. Development of new methods for that purpose is an important task that faces not only FDA but also our European counterparts.

Dr. Pritchett is a Biologist with CVM's Feed Safety Team in the Division of Animal Feeds. Dr. Momcilovic is a Medicated Feed Specialist with CVM's Medicated Feeds Team in the Division of Animal Feeds.

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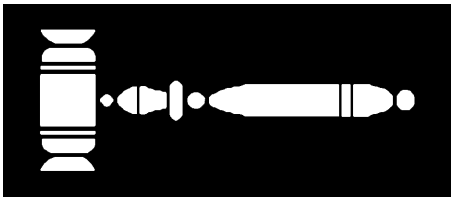
REGULATORY ACTIVITIES



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

- John M. Sterk, Jonal Dairy, Lynden, WA
- Richard C. Iest, Richard Iest Dairy, Madera, CA
- Ronald C. Pietersma, Falloncrest Farms, Chino, CA
- Andy Davis, Davis Dairy Farm, Sterling, CT
- Frank Veenstra, Veenstra Dairy, Hagerman, ID
- Eliseu and Theresa Cunha, Eliseu and Theresa Cunha Dairy, Hanford, CA
- Alvarino F. Alves, Alves Family Dairy, Hilmar, CA

These violations involved illegal residues of gentamicin in dairy cows; sulfadimethoxine in a dairy cow; tetracycline in a cow; tilmicosin, penicillin, and sulfadimethoxine in dairy cows; penicillin in a cow; and gentamicin in a bob veal calf.

In addition, a warning letter was issued to Vernal J. Gomes & D. Stanley Gomes, M.F. Gomes and Sons Dairy, Tulare, CA, for a tissue residue violation in a cow containing sulfadimethoxine. This firm has a history of offering animals for sale for human food use which have been found to be adulterated with drug residues.

Warning letters were sent as a result of violative conditions found during investigations of the following medicated feed manufacturing facilities:

- Kern Livestock Supplement Co., Inc., Bakersfield, CA
- Manna Pro Corporation, Fresno, CA
- Del Mesa Farms, Turlock, CA
- New Vision Co-op, Jeffers, MN
- Master Mix of Puerto Rico, Inc., Hatillo, P.R.

These violations included failure to flush or otherwise clean mixing equipment between batches of feeds medicated with active drug ingredients; failure to investigate the reasons for failed feeds; failure to maintain a complete Master Record File; failure to perform adequate numbers of assays; failure to proofread, date, and sign by a responsible individual incoming master formulas prior to the manufacture of these feeds; failure to repair an inoperable bulk liquid scale; and failure to calibrate production weighing scales to maintain their accuracy.

A warning letter was sent to Diane C. Hansgen, D.V.M., President, Fairfax Veterinary Clinic, Ltd., Fairfax, MN, for a serious deviation of 21 CFR 530, Extralabel Drug Use in Animals. Dr. Hansgen has prescribed enrofloxacin, a fluoroquinolone, for the treatment of young swine. This is a prohibited extralabel use of the drug, since the extralabel use of fluoroquinolones and glycopeptides was prohibited in food-producing animals, effective August 20, 1997.

A warning letter was sent to Marvin G. Moose, Ph.D., Chairman of Ameri-Pac, Inc., Leavenworth, KS, for significant deviations found in the veterinary drug manufacturing facility. These deviations included failure to perform process validation on specific products Hydrogen Peroxide 3%, Kaolin-Pectin, or Bismusal; failure to conduct annual product review; failure to include production steps in the Master Production Record or individual batch records; failure to perform adequate monitoring and microbial testing on the water system; and, lack of written procedures identifying the persons who have quality control authority concerning the acceptance or refusal of product.

A warning letter was also sent to Mr. Joseph M. Weller, President, Nestle/Friskies PetCare Company, Glendale, CA, for serious deviations regarding the safe and proper processing of Low Acid Canned Foods. These deviations caused the firm to distribute and subsequently recall more than 5,500 cases of cat food that had not been retorted. □

DRAFT GUIDANCE ON ANTHELMINTIC EFFECTIVENESS AVAILABLE

The Food and Drug Administration (FDA) announced in the October 19, 2000, *Federal Register*, the availability of three draft guidances for industry entitled "Effectiveness of Anthelmintics: Specific Recommendations for Equine" (#109,) "Effectiveness of Anthelmintics: Specific Recommendations for Porcine'' (#110,) and "Effectiveness of Anthelmintics: Specific Recommendations for Canine'' (#111.) These draft guidances are available for comment only.

These draft guidance documents were developed by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). They are intended to standardize and simplify methods used in the evaluation of new anthelmintics submitted for approval to the European Union, Japan, and the United States.

These three draft guidances should be read in conjunction with the "Efficacy of Anthelmintics: General Recommendations (EAGR)'' announced in the *Federal Register* of July 16, 1999 (*http://www.fda.gov/OHRMS/DOCKETS/98fr/071699a.txt*). The draft guidances for equine, porcine, and canine are part of the EAGR, and the aim of these three draft guidances is to: (1) Be more specific for certain issues not discussed in the general guidance, (2) highlight differences with the EAGR on effectiveness data recommendations, and (3) give explanations for disparities with the EAGR.

These draft guidances represent current FDA thinking on effectiveness recommendations for certain veterinary anthelmintic medicinal products. These draft guidances do not create or confer any rights for or on any person and will not operate to bind FDA or the public. An alternate method may be used as long as it satisfies the requirements of applicable statutes and regulations.

Copies of these documents may be obtained from CVM's Guidelines and Guidances Page (*http://www.fda.gov/cvm/fda/TOCs/guideline.html*) or by calling or writing CVM's Communications Staff at FDA/Center for Veterinary Medicine, HFV-12, 7500 Standish Place, Rockville, MD 20855, 301-594-1755.

Interested persons may submit written comments on the guidance documents to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Comments should be identified with the full title of the guidance document and with Docket number 00D-1532. Comments should be submitted by December 18, 2000 to ensure their adequate consideration in preparation of the final guidance document. General comments on Agency guidance documents are welcome at any time.

Further information about these guidance documents is contained in the October 19 *Federal Register* (*http://www.fda.gov/OHRMS/DOCKETS/98fr/101900d.htm*.) Information on the guidance documents is also available from Dr. Thomas Letonja, Center for Veterinary Medicine (HFV-135), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7576, e-mail: tletonja@cvm.fda.gov. Information regarding the VICH is available from: Dr. Sharon R. Thompson, Center for Veterinary Medicine (HFV-3), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-594-1798, e-mail: sthompso@cvm.fda.gov, or Mrs. Carole R. Andres, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-6524, e-mail: candres1@cvm.fda.gov. □

FDA PROPOSES RULES FOR NADA PRESUBMISSION CONFERENCES

FDA published a proposed regulation to describe the procedures to be followed for requesting, conducting, and documenting presubmission conferences in the August 25, 2000, *Federal Register*. Under the Animal Drug Availability Act (ADAA) amendments to the Federal Food, Drug, and Cosmetic Act, any person intending to file a new animal drug application (NADA), supplemental NADA, or to investigate a new animal drug is entitled to one or more conferences with FDA to reach an agreement establishing a submission or investigational requirement.

A submission or investigational requirement includes, among other things, identification of the number and types of studies that are necessary to demonstrate the safety and effectiveness of a new animal drug for the intended uses and conditions of use prescribed, recommended, or suggested in the proposed labeling for the new animal drug. Presubmission conferences give FDA and a potential applicant a means to identify the least burdensome appropriate requirements that have a reasonable likelihood of resulting in approval.

This proposed regulation describes how a person would request a presubmission conference and describes the procedures for the conduct of the presubmission conference.

Copies of this proposed rule may be obtained from CVM's Home Page on the Internet at: *http://www.accessdata.fda.gov/scripts/oc/ohrms/index.cfm* or by calling or writing the *FDA Veterinarian*.

Further information about this proposed rule is available from Gail L. Schmerfeld, Center for Veterinary Medicine (HFV-100), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-594-1620. □

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Schering-Plough Animal Health Corp. (NADA 141-153)	Diclazuril Bacitracin Methylene Disalicylate (Clinacox™) (BMD®)	Broiler chickens. For the prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	MEDICATED FEED—The NADA provides for the use of the two Type A medicated articles to make Type C medicated broiler feed. The feed is used for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis*, and *E. maxima*. Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Not for use in hens producing eggs for human food. *Federal Register* 08/17/00
Schering-Plough Animal Health Corp. (NADA 141-158)	Diclazuril Bambermycins (Clinacox™) (Flavomycin®)	Broiler chickens. For the prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	MEDICATED FEED—The NADA provides for the use of two Type A medicated articles to make Type C medicated broiler feed. The feed is used for the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mitis*, and *E. maxima*. Because diclazuril is effective against *E. maxima* later in its life cycle, subclinical intestinal lesions may be present for a short time after infection. Not for use in hens producing eggs for human food. *Federal Register* 08/17/00
Schering-Plough Animal Health Corp. (NADA 141-090)	Diclazuril Virginiamycin (Clinacox™) (Stafac®)	Broiler chickens. For the prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	MEDICATED FEED—The NADA provides for use of two Type A medicated articles to make Type C medicated broiler feed. The Type C feed contains 0.91 g/ton diclazuril and 5 or 5 to 15 g/ton virginiamycin. The feed containing 5 to 15 g/ton virginiamycin is used for prevention of coccidiosis and increased rate of weight gain only. Not for use in hens producing eggs for human food. *Federal Register* 08/17/00

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Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 141-155)	Bacitracin Methylene Disalicylate Robenidine Hydrochloride Roxarsone (BMD®) (ROBENZ®) (3-NITRO®)	Broiler chickens. For the prevention of coccidiosis; as an aid in the prevention and control of necrotic enteritis; and for increased rate of weight gain, improved feed efficiency, and improved pigmentation.	MEDICATED FEED—The NADA provides for use of three Type A medicated articles to make a three-way combination Type C medicated broiler feed containing 30 g/ton robenidine hydrochloride, 22.7 to 45.4 g/ton roxarsone, and 50 or 100 to 200 g/ton BMD for use in broiler chickens. The 50 g/ton BMD feeds are used for prevention of coccidiosis; for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broilers; and as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin. The feeds containing 100 to 200 g/ton BMD are used for prevention of coccidiosis; for increased rate of weight gain, improved feed efficiency, and improved pigmentation in broilers; and as an aid in the control of necrotic enteritis caused or complicated by *Clostridium spp.* or other organisms susceptible to bacitracin. Feed continuously as sole ration. Do not feed to layers. Withdraw 5 days before slaughter. *Federal Register* 08/22/00
Alpharma, Inc. (NADA 141-138)	Monensin Bacitracin Methylene Disalicylate Roxarsone (Coban®) (BMD®) (3-NITRO®)	Replacement chickens. Used as an aid in the prevention of coccidiosis, as an aid in the prevention and control of necrotic enteritis, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation.	MEDICATED FEED—The NADA provides for use of approved single ingredient Type A medicated articles to make a three-way combination drug Type C medicated feed for replacement chickens intended as caged layers. The Type C medicated feeds containing 90 to 110 g/ton monensin, 50 or 100 to 200 g/ton BMD, and 22.7 to 45.4 g/ton roxarsone are used as an aid in the prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E acervulina, E. brunetti, E. mivati*, and *E. maxima*; as an aid in the prevention (at 50 g/ton BMD) or control (at 100 to 200 g/ton BMD) of necrotic enteritis caused or complicated by Clostridium spp. or other organisms susceptible to bacitracin; and for increased rate of weight gain, improved feed efficiency, and improved pigmentation. To be fed continuously as sole ration. Do not feed to laying chickens or chickens over 16 weeks of age. Withdraw 5 days before slaughter. Use as sole source of organic arsenic. *Federal Register* 09/05/00

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Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Elanco Animal Health, a Division of Eli Lilly & Co. (NADA 140-955)	Monensin Bambermycins (Coban®) (Flavomycin®)	Turkeys. For prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency in growing turkeys.	MEDICATED FEED—The NADA provides for use of two approved Type A medicated articles to make a 2-way combination Type C medicated feed. The Type C turkey feed containing 54 to 90 g/ton monensin and 1 to 2 g/ton bambermycins are used for prevention of coccidiosis caused by *Eimeria adenoeides, E. meleagrimitis*, and *E. gallopavonis*, and for improved feed efficiency. For growing turkeys only. The Type C turkey feed containing 54 to 90 g/ton monensin and 2 g/ton bambermycins are used for increased rate of weight gain also. Feed continuously as sole ration. Some strains of turkey coccidia may be monensin tolerant or resistant. *Federal Register* 09/05/00
Elanco Animal Health, a Division of Eli Lilly & Co. (NADA 141-164)	Monensin Tylosin Phosphate (Coban®) (Tylan®)	Broiler chickens. Used as an aid in the prevention of coccidiosis, for increased rate of weight gain, and improved feed efficiency.	MEDICATED FEED—The NADA provides for use of approved, single-ingredient Type A medicated articles to make two-way combination Type C medicated broiler feeds. The combination Type C feeds containing 90 to 110 g/ton monensin and 4 to 50 g/ton tylosin are used as an aid in the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati*, and *E. maxima* for increased rate of weight gain, and improved feed efficiency. Feed continuously as sole ration. In the absence of coccidiosis, the use of monensin with no withdrawal period may limit feed intake resulting in reduced weight gain. Do not feed to laying chickens. *Federal Register* 09/05/00
Alpharma, Inc. (NADA 141-139)	Monensin Roxarsone (Coban®) (3-Nitro®)	Replacement chickens. Used as an aid in the prevention of coccidiosis and for increased rate of weight gain, improved feed efficiency, and improved pigmentation.	MEDICATED FEED—The NADA provides for use of approved, single-ingredient Type A medicated articles to make two-way combination drug Type C medicated feed. The Type C feed containing 90 to 110 g/ton monensin and 22.7 to 45.4 g/ton roxarsone are used in the prevention of coccidiosis caused by *E. necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati*, and *E. maxima*, and for increased rate of weight gain, improved feed efficiency, and improved pigmentation. Feed continuously as sole ration. Use as sole source of organic arsenic. Do not feed to laying chickens, or chickens over 16 weeks of age. Withdraw 5 days before slaughter. *Federal Register* 09/08/00

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NEW ANIMAL DRUG APPROVALS (Continued)

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 141-059)	ChlortetracyclineBacitracin Methylene Disalicylate (ChlorMax™) (BMD®)	Swine. For control of porcine proliferative enteropathies (ileitis) and for increased rate of weight gain and improved feed efficiency.	MEDICATED FEED—The NADA provides for use of approved, single-ingredient chlortetracycline and bacitracin methylene disalicylate Type A medicated articles to make two-way combination Type C medicated feeds for use in growing and finishing swine. The Type C feed containing approximately 400 g/ton CTC (to provide 10 mg/lb BW) and 10 to 30 g/ton BMD are used for the control of ileitis caused by Lawsonia intracellularis susceptible to chlortetracycline. Should not be fed for more than 14 days. *Federal Register* 09/08/00
Roche Vitamins, Inc. (NADA 140-865)	Narasin Bacitracin Zinc (Monteban®) (Baciferm®)	Broiler chickens. For the prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	MEDICATED FEED—The NADA provides for use of approved Type A medicated articles to make combination Type C medicated feeds. The Type C feed containing 54 to 72 g/ton narasin and 4 to 50 g/ton bacitracin zinc are used for prevention of coccidiosis caused by *Eimeria necatrix, E. tenella, E. acervulina, E. brunetti, E. mivati*, and *E. maxima*, and for increased rate of weight gain and improved feed efficiency. For broilers only. Feed continuously as sole ration. Do not allow adult turkeys, horses, or other equines access to formulations containing narasin; ingestion by these species has been fatal. *Federal Register* 09/15/00

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ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Med-Pharmex, Inc. (ANADA 200-289)	Neomycin Sulfate Oral Solution (NEORAL®)	Cattle, swine, sheep, goats. For the treatment and control of colibacillosis.	ORAL—The ANADA is a generic copy of Pharmacia & Upjohn's NADA 011-315, NEOMIX® 325 soluble powder. *Federal Register* 09/05/00
Agri Laboratories, Ltd. (ANADA 200-271)	Levamisole Phosphate Injectable Solution 13.65%	Cattle. For the treatment of various species of gastrointestinal parasites.	SUBCUTANEOUS—The ANADA is a generic copy of Schering-Plough Animal Health's NADA 126-742 for LEVASOLE® Injection. *Federal Register* 10/16/00

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Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Combe, Inc. (NADA 5-236)	2-Mercaptobenzothiazole Solution (Sulfodene®)	Dogs. Used as an aid in treatment of certain common skin inflammations.	TOPICAL—The supplement provides for revisions to labeling by removing the phrase "treating moist dermatitis and hot spots" and by adding in its place the phrase " the treatment of hot spots (moist dermatitis)". *Federal Register* 08/22/00
Hoechst Roussel Vet (NADA 131-675)	Fenbendazole (Safe-Guard® 20%)	Turkeys, Cattle, Swine, Zoo and wildlife animals. For the removal and control of gastrointestinal worms.	MEDICATED FEED—The supplemental NADA provides for the use of approved fenbendazole Type A medicated articles to make Type B and Type C medicated turkey feed containing 14.5 g/ton fenbendazole for removal and control of round worms, cecal worms in growing turkeys. Additionally tolerances are established for fenbendazole sulfone in turkey liver and muscle. A 3-year marketing exclusivity applies to the new species (turkey) for which the supplemental application was approved. Feed continuously as sole ration for 6 days. *Federal Register* 08/22/00
Pharmacia and Upjohn Co. (NADA 141-036)	Pirlimycin Hydrochloride (PIRSUE®)	Dairy Cattle. For treatment of clinical and subclinical mastitis in lactating dairy cattle.	INTRAMAMMARY—The supplement provides for treatment of clinical and subclinical mastitis in lactating dairy cattle caused by *Staphylococcus species* and *Streptococcus species*; for reduction in the pre-slaughter withdrawal period from 28 days to 9 days; and for revision of the milk discard statement in labeling to state the 36-hour milk discard time only (i.e., to remove reference to the number of milkings). Also an ADI for total pirlimycin residues and a tolerance for residues in cattle muscle are established. A 3-year exclusivity period is established for the new formulation that is the subject of this supplemental application. *Federal Register* 10/16/00 □

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HEALTH & HUMAN SERVICES

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Food and Drug Administration
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