The Warning Letters presented in this chapter were chosen to provide examples of the types of Warning Letters issued for violations of FDA laws. A complete list of Warning Letters issued is available on FDA's web site at: http://www.fda.gov/foi/warning.htm.

Bovine Spongiform Encephalopathy (BSE) Feed Ban

Title 21, Code of Federal Regulations (CFR), Part 589, Section 2000 (21 CFR 589.2000)
Animal Proteins Prohibited in Ruminant Feed.

This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy (BSE). The use of protein derived from mammalian tissues, as defined by 21 CFR 589.2000(a)(1), as an animal feed ingredient or in animal feeds must comply with the requirements of 21 CFR 589.2000. Products that contain or may contain protein derived from mammalian tissues and that are intended for use in animal feed (prohibited material) must be labeled with the cautionary statement, “Do not feed to cattle or other ruminants."

FDA maintains a Web Page devoted entirely to the topic of BSE. To view the Web Page go to: http://www.fda.gov/oc/opacom/hottopics/bse.html.

Report on FDA's Dallas District Investigation of Bovine Spongiform Encephalopathy Event in Texas

On June 24, 2005, the U.S. Department of Agriculture (USDA) informed FDA that a cow in Texas tested positive for Bovine Spongiform Encephalopathy (BSE). Information provided by USDA's Animal and Plant Health Inspection Service (APHIS) was that the BSE positive cow was born and raised in a herd in Texas and was approximately 12 years old. The animal was sampled for BSE at a pet food plant in Texas on November 15, 2004, as part of USDA’s enhanced surveillance program. The animal was disposed of by incineration and did not enter the human food or animal feed chains.

Although the positive animal posed no risk to the animal feed supply, FDA, APHIS, the Texas Animal Health Commission (TAHC), and the Texas Feed and Fertilizer Control

Service (TFFCS) conducted a feed investigation with two main objectives. The first objective was to identify all protein sources in the animal's feed history that could potentially have been the source of the BSE agent. The second objective was to verify that cattle leaving the herd after 1997 that were identified by USDA/APHIS as animals of concern (e.g. progeny and feed cohorts), were rendered at facilities in compliance with the regulation that prohibits most mammalian protein in feed for ruminants (21 CFR 589.2000, which became effective August 4, 1997, herein called the BSE/Ruminant Feed rule).

The feed history investigation identified 21 feed products that had been used on the farm since 1990. These feed products were purchased from three retail feed stores and had been manufactured at nine different feed mills. The investigators visited these establishments to collect information on formulations, shipping invoices, and use of ruminant meat and bone meal (MBM) on the premises both prior to the 1997 BSE/Ruminant Feed rule and after. This investigation found no feed products used on the farm since 1997 that had been formulated to contain prohibited mammalian protein.

The investigation identified one feed which contained an animal protein source that could not be identified. The investigation also found one feed mill that supplied feed to the farm that had used ruminant MBM in feed formulations for non-ruminant species after the BSE/Ruminant Feed rule went into effect, which is permitted under the rule, and that several feed mills had used ruminant MBM in feeds prior to the feed ban. Although the investigation did not identify a specific feed source as the likely cause of this animal's infection, it is probable that the most likely route of exposure for this animal was consumption of an animal feed containing mammalian protein prior to the implementation of the BSE/Ruminant Feed rule in 1997.

The investigation into the disposition of herd mates from this farm involved visits to nine slaughter plants and eight rendering plants. The investigation found that all rendering plants were operating in compliance with the BSE/Ruminant Feed rule. A review of the inspection history of each of these rendering firms found no violations.

To read the complete report on this investigation which is available on FDA's Web Site go to: http://www.fda.gov/cvm/texasfeedrpt.htm.

Warning Letter Issued to A & A Services

FDA Inspection Found Firm Not Properly Labeling Products with Required Cautionary Statement

On April 6, 2005, FDA's San Francisco District Office issued a Warning Letter to A & A Services, Kapolei, Hawaii. FDA's inspection on January 10 - 11, 2005, found significant deviations from FDA regulations.

FDA's inspection found that the firm was not properly labeling the products it distributed to swine farms, which contained food waste from restaurants and hospital cafeterias, with the required cautionary statement. The inspection also found that the same containers were being used to hold both prohibited materials to be used for feed for non-ruminants and non-prohibited materials to be used for feed for ruminants. In addition, the firm failed to provide written procedures specifying clean-out procedures or other measures to avoid cross-contamination of the feed products to be used for ruminants.

Warning Letter Issued to Anamax Corporation for Cross-Contamination in Processing Feeds

On June 6, 2005, FDA's Minneapolis District Office issued a Warning Letter to Anamax Corporation, Green Bay, Wisconsin. FDA's inspection on January 12-20, 2005, found significant deviations from FDA regulations.

FDA's inspection found that the operation failed to provide measures to prevent commingling or cross-contamination in that the plant failed to maintain written procedures or to use clean-out procedures that were adequate to prevent carryover of protein derived from mammalian tissues into feeds that may be used for ruminants. The inspection also found that the firm failed to label products with the cautionary statement, "Do not feed to cattle or other ruminants."

Drug Residues in Edible Animal Tissue

Consent Decree of Injunction - Alvin Souza Dairy

On April 13, 2005, the U.S. Attorney's Office in the Eastern District of California filed a Consent Decree of Permanent Injunction against Alvin L. Souza, an individual doing business as Alvin Souza Dairy, Tulare, California, that will require the defendant to

implement systems to prevent illegal residues of drugs in animals sent to slaughter.

The Consent Decree requires the defendant to implement a means of identifying animals treated with animal drugs and not suitable for slaughter and segregating or quarantining them, keeping medication and treatment records, accounting for drug use, and following label directions when using drugs on the animals.

The defendant's animals were found to have numerous illegal drug residues caused by the failure of Mr. Souza and the firm to maintain controls to prevent illegal residues in animals delivered for slaughter.

Leading up to the injunction, investigators reported 13 illegal tissue residues in edible tissues of seven animals sampled by the U.S. Department of Agriculture's Food Safety and Inspection Service between December 1997 and January 2004. Inspectors found illegal residues of antibiotics such as penicillin, gentamicin, neomycin, and sulfadimethoxine. Some of the drug residues were above tolerance levels. For other drugs, though, the FDA has not established a tolerance level, so any detectable residue of these drugs is a violation of the FDA regulations.

FDA's San Francisco District conducted the investigation that led to this Consent Decree.

Consent Decree of Injunction - White River Dairy

Inspection Found Numerous Illegal Drug Residues including Penicillin, Gentamicin, Tylosin, and Sulfadimethoxine

On July 15, 2005, a Consent Decree of Permanent Injunction was filed in the U.S. District Court for the Eastern District of California against Carl M. Sousa, an individual doing business as White River Dairy. Mr. Sousa is a livestock producer who delivered animals for sale for slaughter as human food. This action was based on the numerous illegal drug residues caused by Mr. Sousa, and the poor management practices that had been the primary source of these illegal drug residues.

From February 1, 1999-December 23, 2003, nine illegal drug residues were found by USDA, including antibiotics such as penicillin, gentamicin, tylosin, and sulfadimethoxine that were above the permitted tolerance levels and residues of drugs which are not permitted at any level. FDA was/is concerned about the sale of animals for slaughter for human food that may contain illegal levels of animal drugs because of their potential for adverse effects on human health.

Under the terms of the Consent Decree, the defendants must implement residue avoidance systems including segregation/quarantine, and identifying treated animals and the source of

each animal that they purchase or transport, maintaining medication/treatment and drug inventory/accountability records, and following label directions for use including drug withdrawal times prior to slaughter.

Warning Letters Issued for Illegal Drug Residues

Dihydrostreptomycin

On September 28, 2005, FDA's Buffalo District Office issued a Warning Letter to Silver Spring Farm, Syracuse, New York, for offering an animal for sale as human food in violation of the Act.

FDA's investigation on August 12 and 15, 2005, confirmed that an animal was offered for sale for slaughter as food that contained illegal drug residues. The inspection also revealed that the new animal drug penicillin-dihydrostreptomycin in oil was adulterated and unsafe.

In June 2005, a dairy cow was consigned for slaughter as food, and slaughtered. U.S. Department of Agriculture (USDA) analysis of tissue samples collected identified the presence 6.37 ppm dihydrostreptomycin in kidney tissue. A tolerance of 2 ppm has been established for residues of dihydrostreptomycin in uncooked, edible kidney tissue of cattle. The presence of this drug in edible tissue caused the food to be adulterated.

FDA's investigation found that animals were held under conditions so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply. Food from animals held under such conditions are adulterated.

FDA's investigation found that the extralabel use failed to comply with FDA's regulations.

Flunixin

On November 2, 2004, FDA's Seattle District Office issued a Warning Letter to Rhody Dairy, Sumas, Washington, for offering an animal for sale for food that contained illegal drug residues.

On December 8, 2003, a dairy cow was identified for slaughter as human food. USDA analysis of tissue samples collected from the cow identified the presence of flunixin at 0.21 ppm (210 ppb) in the liver. At the time Rhody Dairy offered the cow for sale, flunixin had not yet been approved for use in lactating dairy cattle. The presence of flunixin in the liver of this dairy cow indicated that the firm treated this cow with flunixin and that this use did not conform to the then-approved use, or the extralabel use regulations. This caused the animal drug to be unsafe and adulterated.

In addition, the presence of flunixin residues caused the food to be adulterated because it contained a new animal drug that is unsafe.

Flunixin was approved for use in lactating dairy cows as of August 19, 2004. The established tolerance of flunixin in cattle is 0.125 ppm in the liver. Even if flunixin had been approved for use in lactating dairy cattle at the time the cow was offered for sale, the residue of flunixin in the cow (0.21 ppm or 210 ppb) would have exceeded the tolerance set for flunixin in cattle (0.125 ppm or 125 ppb).

FDA's investigation in June 2004, also found that animals at this facility were held under conditions that were inadequate to prevent animals bearing potentially harmful drug residues from entering the food supply. For example:

- There was no adequate system for determining the medication status of animals offered for slaughter.
- There was no adequate system to assure that medicated animals were withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs in edible tissues.
- There was no adequate system to ensure that drugs were used in a manner not contrary to the directions contained in their labeling.

Gentamicin

On November 23, 2004, FDA's Detroit District Office issued a Warning Letter to Thuemmel Dairy, Inc., Port Austin, Michigan, for offering an animal for sale for food that contained illegal drug residues.

FDA's inspection on June 29, 2004, found that gentamicin sulfate was adulterated because the drug was used in a manner that did not conform with the extralabel use regulations in 21 CFR Part 530.

On May 12, 2004, an adult dairy cow from Thuemmel Dairy was identified for slaughter as human food and slaughtered. USDA analysis of tissue samples collected identified the presence of gentamicin in the kidney and liver.

On June 1, 2004, an adult dairy cow from Thuemmel Dairy was identified for slaughter as human food, and slaughtered on June 2, 2004. USDA analysis of tissue samples collected identified the presence of gentamicin in the kidney.

There is no approved tolerance level for gentamicin in dairy cattle. The presence of this drug in edible tissue from these animals caused the food to be adulterated.

Animals were held under conditions which were inadequate in that medicated animals bearing potentially harmful drug residues are likely to enter the food supply. The farm did not maintain adequate medication/treatment records to identify the animal, date of medication, the drug dosage administered, and the drug pre-slaughter withdrawal time.

Gentamicin sulfate was adulterated in that it was used in dairy cattle, a species for which it is not approved. The extralabel use of an approved animal drug is allowed if the use complies with the Act and FDA regulations. However, the use of the drug was not in compliance with the extralabel use regulations because it was administered without the benefit of a valid veterinarian client-patient relationship. The use of gentamicin resulted in the presence of drug residue in edible tissue that might present a risk to public health.

Neomycin

On February 28, 2005, FDA's San Juan District Office issued a Warning Letter to Vaqueria Gustavo Toledo, Hatillo, Puerto Rico, for offering five animals for sale for slaughter as food in violation of the Act. FDA’s investigation on September 28-October 5, 2004, revealed that an animal drug used on the farm was determined to be unsafe and adulterated because the drug was used in a manner that did not conform with its approved use or the regulations for Extralabel Drug Use in Animals.

These five animals in question were sold by an intermediary for slaughter as human food. USDA analysis of tissue samples revealed the presence of neomycin residues in the kidney in each of the five animals. The presence of the drug in edible tissues at the reported levels caused the food to be adulterated.

FDA’s investigation found that animals were held under conditions which were so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply. Foods from animals held under such conditions are considered adulterated.

The drug neomycin was adulterated when it was used at a dosage level that is contrary to the product's approval. Neomycin was administered without the supervision of a licensed veterinarian, and the use of neomycin resulted in the presence of drug residue in edible tissue that might present a risk to public health.

Oxytetracycline

On October 20, 2004, FDA's Seattle District Office issued a Warning Letter to Cedar Arch-North, Firth, Idaho, for introduction of an animal for sale for food that contained illegal drug residues. FDA’s inspection on August 2 and 3, 2004, revealed that the farm had used an animal drug determined to be unsafe.

In May 2004, the farm offered for sale a cow for slaughter as human food. USDA analysis of tissue samples collected identified the presence of oxytetracycline at 84.99 ppm in the kidney, 42.76 ppm in the liver, and 12.85 ppm in the muscle. A tolerance of 12 ppm has been established for residues of oxytetracycline in kidney tissue, 6 ppm in liver tissue, and 2 ppm in muscle tissue. USDA analysis identified the presence of sulfadimethoxine at 1 ppm in the liver and 1.47 ppm in muscle tissue. The tolerance for sulfadimethoxine in edible tissue is 0.1 ppm. The presence of these drugs in excess of the established tolerances in the edible tissues caused the food to be adulterated.

FDA's investigation also found that animals were held on the farm under conditions that were so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply.

The oxytetracycline amphoteric injectable was used it to treat a dairy cow contrary to the product's approved labeling. Oxytetracycline was administered in excess of the labeled dose without a prescription for such use. The extralabel use of an approved drug is allowed if the use complies with the Act and FDA regulations. However, this extralabel use was not in compliance. The drug was therefore unsafe and adulterated.

FDA noted that this was not the first residue associated with the farm. On or about August 1998, October 1998, and February 1997, the farm offered for sale cattle as human food. USDA analysis of tissue samples collected from these animals identified the presence of sulfadimethoxine in excess of the established tolerances for edible tissue.

Penicillin G. Procaine and Sulfadimethoxine

On November 8, 2004, FDA's Dallas District Office issued a Warning Letter to Spandet Dairy, Inc., Hart, Texas, for introducing an animal for sale for food that contained illegal drug residues.

FDA's investigation revealed that the dairy treated a cow with penicillin G. procaine and sulfadimethoxine. The cow was treated for a retained placenta following delivery of her calf and for diarrhea on January 31-February 19, 2004. The cow was sold and subsequently offered for slaughter as human food in February 2004. USDA analysis of tissue samples collected from the cow identified the presence of penicillin in the kidney at 0.21 ppm, and sulfadimethoxine in the liver at 0.11 ppm. The tolerance for penicillin is 0.05 ppm in the uncooked edible tissues of cattle, and the tolerance for sulfadimethoxine is 0.1 ppm in the uncooked edible tissues of cattle. The presence of these drugs, at the reported levels, in the edible tissues of this animal, caused the food to be adulterated.

FDA's investigation from June 23-25, 2004, found that animals were held under conditions which were so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply. For example:

- There was no adequate system for assuring that animals were withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues.

- There was no adequate system for determining the medication status of animals offered for slaughter. The medical records did not include the route of drug administration or dosage administered and did not identify who administered the drug.

Penicillin G procaine was adulterated when the drug was not used in conformance with its approved labeling or on the order of a licensed veterinarian. Use of the drug without following the dosage level, duration of treatment, frequency of treatment, and withdrawal period of either the approved labeling or the order of the veterinarian caused the drug to be unsafe. Extralabel drug use is permitted only in conformance with all criteria in 21 CFR Part 530, including that there be no residue above established tolerance levels. Because this extralabel use of penicillin resulted in the presence of a residue above the established tolerance, use was not in compliance with the extralabel use regulations.

Penicillin

On December 22, 2004, FDA's Minneapolis District Office issued a Warning Letter to Huebner Farm, Columbus, Wisconsin, for offering an animal for sale for food that contained illegal drug residues. FDA's inspection on September 7, 2004, found the adulteration of a new animal drug because the drug was used in a manner that did not conform with its approved use or extralabel use regulations, therefore making it unsafe.

In February 2004, a cow from Huebner Farm was identified for slaughter as human food, sold and slaughtered. FDA's inspection documented that penicillin was used to medicate animals at this dairy operation. USDA analysis of tissue samples collected from the animal sold identified the presence of 0.28 ppm penicillin in the kidney. A tolerance of 0.05 ppm has been established for residues of penicillin in the uncooked edible tissues of cattle. The presence of this drug in edible tissue from this animal caused the food to be adulterated.

The investigation also found animals were held under conditions that were inadequate to prevent animals bearing potentially harmful drug residues from entering the food supply.

- There was no adequate system for determining the medication status of animals and assuring that medicated animals were withheld from slaughter for the appropriate period of time to deplete potentially hazardous residues of drug.

- The farm's medication records did not contain the name of the drug administered, the amount of drug administered, the identity of the individual administering the drug, or the pre-slaughter withdrawal times.

Sulfadimethoxine

On March 11, 2005, FDA's Minneapolis District Office issued a Warning Letter to Elder Grove Dairy Farm, Colby, Wisconsin, for a dairy cow for sale for food that contained illegal drug residues. FDA's investigation from January 24-27, 2005 revealed that a new animal drug was used that was determined to be unsafe and adulterated.

In October 2004, a dairy cow from Elder Grove Dairy Farm was identified for slaughter as human food. USDA analysis of tissue samples collected from the animal identified the presence of sulfadimethoxine in the liver at 5.82 ppm and in the muscle at 3.65 ppm. The tolerance for sulfadimethoxine in edible tissues of cattle is 0.10 ppm.

The following conditions were noted:

- There was no adequate system for determining the medication status of animals offered for slaughter.
- There was no adequate system for assuring that medicated animals had been withheld from slaughter for appropriate periods of time to deplete potentially hazardous residues of drugs.
- There was no adequate system for assuring that drugs were used in accordance with their labeling.

Medicated Feeds

Warning Letter Issued to Suther Feeds

Deviations from CGMPs Could Cause Medicated Feeds to be Contaminated with Residual Drugs

On October 20, 2004, FDA's Kansas City District Office issued a Warning Letter to Suther Feeds, Inc., Frankfort, Kansas, for significant deviations from Current Good Manufacturing Practice regulations for Medicated Feeds. These deviations were revealed during FDA's inspection in August 2004. Such deviations caused the feeds being manufactured at this facility to be adulterated.

FDA's investigation found deviations including, but not limited to, the following:

- Failure to ensure that equipment that came in contact with active drug components and feeds in process was subject to all reasonable and effective procedures to prevent unsafe contamination of manufactured feed.

- Failure to conduct sequential production of medicated feeds on a predetermined basis designed to prevent unsafe contamination of feeds with residual drugs.
- Failure to investigate and implement corrective action when assay results showed medicated feeds were not within permissible assay limits.
- Failure to maintain master records and batch production records.
- Failure to maintain distribution records for each shipment of medicated feed.
- Failure of the firm's mixer/blender study to demonstrate the equipment's capability to produce a medicated feed of intended potency.
- Failure to maintain equipment in a reasonably clean and orderly manner.

Warning Letter Issued to West Feeds

Medicated Feed Mill Did Not Have Required License to Manufacture Medicated Feeds

On April 1, 2005, FDA's Seattle District Office issued a Warning Letter to West Feeds, Inc., Billings, Montana, for significant deviations from FDA regulations. These deviations caused the medicated feeds being manufactured at the facility to be adulterated.

The deviations documented in the Warning Letter are as follows:

- Failure to conduct periodic assays on an annual basis on at least three samples of medicated feeds requiring a medicated feed mill license, for each drug or drug combination used.
- Failure to have a medicated feed mill license although the firm was manufacturing medicated feeds from a Category II Type A medicated article.

Warning Letter Issued to Archer Daniels Midland Feed Mill

On January 14, 2005, FDA's Kansas City District Office issued a Warning Letter to Archer Daniels Midland (ADM) Company, Decatur, Illinois. FDA's inspection on July 27-August 6, 2004, revealed significant deviations from FDA regulations.

The deviations observed during the inspection included, but were not limited to the following:

- Failure to assure that the equipment used in the manufacture of Type A Medicated Articles is operated in a manner that ensures the integrity of the finished product.

- Failure to adequately store incoming bulk drug components in a manner that assures the maintenance of their identity, strength, quality, and purity.

Veterinary Drugs

Illegal Dispensing of Veterinary Prescription Drugs

Warning Letters Issued to Firms for Failure to Obtain Lawful Orders from Licensed Veterinarian

Prime Veal Feed, Ltd.

On December 15, 2004, FDA's Cincinnati District Office issued a Warning Letter to Prime Veal Feed, Ltd., Kensington, Ohio, for selling and dispensing veterinary prescription drug products without a lawful order from a licensed veterinarian. Because the firm dispensed prescription new animal drugs without a lawful written or oral order from a licensed veterinarian while held for sale, the drugs were misbranded.

On August 16-September 3, 2004, FDA's inspection of the feed mill revealed that the firm was selling and dispensing veterinary prescription drug products without a lawful order from a licensed veterinarian; thereby causing the new animal drugs to be misbranded. Examples of prescription veterinary drugs the firm dispensed without an order from a licensed veterinarian included: Banamine (flunixin meglumine); Micotil (tilmicosin); and Nuflor (florfenicol).

The prescription veterinary drugs were misbranded because they did not bear adequate directions for use, and they do not fall into an exception to that requirement. FDA has defined "adequate directions for use" as "directions under which the layman can use a drug safely and for the purposes for which it is intended." Directions under which a layperson can safely use prescription animal drugs cannot be written because such drugs can only be used safely under the professional supervision of a licensed veterinarian.

These drugs were not exempt because they were not sold by or upon the lawful written or oral order of a licensed veterinarian in the course of the veterinarian's professional practice.

Flunixin Meglumine Injection was dispensed bearing a Dexamethasone label and Selenium-Vitamin E Injection (Mu-Se) bearing an Amoxicillin label. The drugs were misbranded because the labeling was false or misleading, and because they were offered for sale under the name of another drug.

FDA's inspection found that the firm might have been dispensing human prescription drugs, such as Sulfamethoxazole and Trimethoprim tablets, Cephalexin capsules, and Amoxicillin capsules, for extralabel use in animals.

Asociacion de Productores de Leche Camuy-Quebradillas

On June 13, 2005, FDA's San Juan Office issued a Warning Letter to Asociacion de Productores de Leche Camuy-Quebradillas, Camuy, Puerto Rico, for selling and dispensing veterinary prescription drug products without a lawful order from a licensed veterinarian, which caused the products to be misbranded.

On December 16 and 20, 2004, FDA's inspection revealed that the firm was selling and dispensing prescription animal drug products without a lawful order from a licensed veterinarian. Examples of prescription animal drugs the firm dispensed without an order from a licensed veterinarian included: gonadorelin diacetate tetrahydrate sterile solution (Cystorelin); dinoprost tromethamine injection (Lutalyse); and isoflupredone acetate sterile aqueous suspension (Predef).

The prescription animal drugs dispensed by the firm were misbranded because they did not bear adequate directions for use and they did not fall into an exception to that requirement. These drugs are not exempt because they were not sold by or upon the lawful written or oral order of a licensed veterinarian in the course of the veterinarian's professional practice.

Warning Letter Issued to Morris Veterinary Center for Veterinary Prescription Violations

On July 25, 2005, FDA's Minneapolis District Office issued a Warning Letter to Morris Veterinary Center, Morris, Minnesota, for causing animal drugs to be unsafe and adulterated because Morris Veterinary Center was prescribing drugs for use in a manner that did not conform with their approved uses or the regulations for Extralabel Drug Use in Animals.

From April 26 - 28, 2005, FDA's investigation revealed that animal drugs were being prescribed in a manner that caused them to be unsafe and adulterated because the prescribed uses for the drugs did not conform with their approved uses or the regulations for Extralabel Drug Use in Animals.

For example, sulfadimethoxine 40% injection was prescribed in an extralabel manner (i.e., for toxic mastitis) in lactating dairy cattle. The extralabel use of sulfonamide drugs (such as sulfadimethoxine) in lactating dairy cattle is prohibited. In addition, oxytetracycline was prescribed for use in lactating dairy cattle, which is an extralabel use, without meeting FDA regulations.

Sulfadimethoxine and oxytetracycline animal drugs were unsafe and adulterated because they were prescribed for extralabel use that did not comply with the regulations for Extralabel Drug Use in Animals.

Warning Letter Issued to Cattlesmyth Veterinary Service, LLC, for Veterinary Prescription Violations

FDA Inspection Disclosed Veterinary Practice Compounded and Prescribed Products that Did Not Conform to Their Approved Use or the Regulations for Extralabel Drug Use in Animals

On February 24, 2005, FDA's Minneapolis District Office issued a Warning Letter to Cattlesmyth Veterinary Service, LLC., Coleman, Wisconsin, for causing animal drugs to be unsafe and adulterated because the drugs were used in a manner that did not conform with their approved uses or the regulations for Extralabel Drug Use in Animals.

FDA's investigation on October 26 and November 2, 2004, documented that the Cattlesmyth Veterinary Service compounded and prescribed for extralabel use a product ("K LMT") intended for intra-mammary infusion to treat mastitis in dairy cows. The product contained a combination of sulfamethoxazole, trimethoprim, gentamicin sulfate, LS-50 (lincomycin and spectinomycin), dexarnethasone, and, on at least one occasion, dimethyl sulfioxide. The

extralabel use of approved veterinary or human drugs in animals is permitted only if it complies with FDA regulations. The veterinary practice failed to comply with FDA regulation 21 CFR Part 530 in that:

- Sulfamethoxazole is prohibited for extralabel use in lactating dairy cattle.
- The labeling was not legible and could not assure the safe and proper use of the product.
- The labeling lacked information required, such as the established name of each active ingredient (trimethoprim was omitted), and directions for use that included identification of the cattle being treated with the drug, the dosage, frequency, route of administration, and duration of therapy.

- The label for "K LMT" was not entirely legible, especially for what appeared to be the specified withdrawal for milk, which is required to be on the label.
- The requirement that the drug bear or be accompanied by labeling information adequate to assure the safe and proper use of the product was not met.
- A log of extralabel use was not recorded or maintained.

Prior to prescribing or dispensing an animal or human drug for extralabel use in food-producing animals, a substantially extended withdrawal period must be established, supported by appropriate scientific information. "K LMT" labeled withdrawal time of 21 days for meat was not supported by its use in this case.

Because the requirements in compounding, prescribing, and dispensing animal drugs were not met, the Cattlesmyth Veterinary Service's clients used new animal drugs in an unapproved manner without meeting the requirements for extralabel use, thereby rendering the drugs unsafe and adulterated.

Veterinary Pharmaceutical Drug Manufacturing

Warning Letter Issued to Boehringer Ingelheim Vetmedica, Inc. for Violations of CGMPs for Animal Drugs

FDA Inspection Revealed Procedures Designed to Prevent Microbiological Contamination of Drug Products Were Not Followed

On October 20, 2004, FDA's Kansas City District Office issued a Warning Letter to Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Missouri, for significant deviations from current good manufacturing practices for animal drugs (CGMPs). These deviations were revealed during FDA's inspection of veterinary pharmaceutical manufacturing operations from July 19-29, 2004.

These deviations caused the drug products to be adulterated because the methods used in, or the facilities or controls used for, the manufacture, processing, packing, and holding of drugs do not conform with CGMP requirements to assure that such drugs meet the requirements of the Act as to safety, and have the identity and strength, and meet the quality and purity characteristics, which they purport or are represented to possess. The following are examples of the significant deficiencies observed during the inspection:

- Failure to have adequate sampling and testing to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

- Failure to adequately record process details, including sample size and method of collection, to demonstrate Oxytetracycline HC s tested in accordance with the validation protocol and approved methods.
- Documentation did not substantiate rigorous in-process testing was conducted to demonstrate the effectiveness and reproducibility of the process. The sample size used for testing was not always statistically significant.
- Failure to perform thorough investigations of specific failures or unexplained discrepancies and/or make a written record of investigations, including the conclusions and follow-up.
- Procedures designed to prevent microbiological contamination of drug products purporting to be sterile were not followed.
- Not all personnel who enter the sterile core were monitored each day.
- Written procedures describing the handling of all written and oral complaints regarding a drug product were not followed.
- Complaint records reviewed during this inspection were found to be deficient.

FDA Requested Class I Recall: ProHeart 6

The recall of ProHeart 6 was an FDA-requested recall in September/October 2004. ProHeart 6 (moxidectin/moxidectine) Sustained Release Injectable for Dogs is indicated for use in dogs six months of age and older for the prevention of heartworm disease. ProHeart 6 is an injectable product that provides a sustained release of moxidectin, the active ingredient, for six months in the dog for the prevention of heartworm disease. During the period between June 2001 and August 2004, FDA received approximately 5,500 serious adverse event reports on this product. In addition, approximately 565 deaths in dogs have been associated with ProHeart 6. In a meeting with then Acting FDA Commissioner Crawford and the firm, Dr. Crawford requested the firm to recall the product.

Class I Recall: Elanco Brand Micotil 300 Injection

On March 14, 2005, Eli Lilly and Company, Indianapolis, Indiana, initiated a recall of Elanco brand Micotil 300 (Tilmicosin) injection because the client information sheet, which warns of death if the product is injected into humans, was not included in the package. There were two human deaths due to individuals injecting themselves with Elanco brand Micotil 300 (Tilmicosin) injection. Therefore, in January 2004, Elanco committed to FDA that the

product would have updated safety information on the label and a client information sheet. The new warning was that death would result if the product was injected into humans. The lot that was recalled was sold with the warning on the package, but without the client information sheet. The client information sheet warns of death if the product is injected into humans, and provides awareness and understanding of the safe handling information and proper use of Micotil by all new and potential end users in an easy-to-read format. Without the client information sheet, it is possible that serious human health hazard exposure may occur.

Veterinary Pharmacy Compounding

Warning Letter Issued to Lowlyn Pharmacies, Inc.

FDA Inspection Revealed a Significant Number of Compounded Veterinary Drugs Appeared to Be Compounded Outside the Context of a Valid Veterinarian-Client-Patient Relationship

On October 19, 2004, FDA's Dallas District Office issued a Warning Letter to Lowlyn Pharmacies, Inc., Blanchard, Oklahoma, for compounding veterinary drugs using bulk active pharmaceutical ingredients (APIs), which were unsafe since they were not the subject of approved New Animal Drug Applications.

FDA's inspection on May 17 and 26, 2004, confirmed that Lowlyn Pharmacies, Inc., was compounding and distributing veterinary drugs, including Nitrofurazone, Enrofloxacin HCL, Omeprazole, Gentamycin Sulfate, Chlorpromazine HCL, Flunixin Meglumine, and Diclazuril. The drugs were compounded using bulk APIs. FDA is greatly concerned about veterinarians and pharmacies that are engaged in manufacturing and distributing unapproved new animal drugs in a manner that is clearly outside the bounds of a traditional pharmacy practice and that violates the Act. An example is compounding that is intended to circumvent the drug approval process and provide for the mass marketing of products that have been produced with little or no quality control or manufacturing standards to ensure the purity, potency, and stability of the product.

A significant number of the compounded veterinary drugs at this facility appeared to be compounded outside the context of a valid veterinarian-client-patient relationship for administration by an end user. There appeared to be sales to veterinarians for use as office stock in their professional practice and/or for further distribution.

Some of the compounded prescription veterinary drugs were duplicates of FDA-approved animal drug products available on the market, and others had only slightly different dosages

and/or concentrations than FDA approved animal drugs.

FDA was concerned that the drugs being compounded could be used in food producing animals and, therefore, could result in unsafe drug residues in edible tissues. This was true even for products labeled “EQUINE USE ONLY” since horses may be offered for slaughter for food. At least two of the drugs that were being compounded, nitrofurazone and diethylstilbestrol, were not permitted for extralabel use in food producing animals because they presented a risk to public health.