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CVM's HOME PAGE MOVES

The Center for Veterinary Medicine's Home Page on the World Wide Web (WWW) has moved to a new location. The new address is in effect now. The new location for the Home Page is:

http://www.fda.gov/cvm

The old address was:

http://www.cvm.fda.gov

The CVM Home Page continues to include the latest news from the Center; many guidance documents, CVM UPDATES, and other publications; general information about the Center; Freedom of Information (FOI) summaries for recently approved new animal drugs; answers to frequently asked questions; and much more.

CVM CONCERNS ABOUT ANTIMICROBIAL USE IN FOOD ANIMALS

CVM is concerned that the use of therapeutic antimicrobial drugs in food animals will create antimicrobial drug resistance that could contribute to drug-resistant human pathogen bacteria. CVM is discussing these issues with other parts of the U.S. FDA and the U.S. Centers for Disease Control and Prevention (CDC).

CVM agrees with the following points:

1. There is a legitimate need for both older and newer antimicrobial drugs in animal agriculture.

2. The bulk of *Salmonella, E. coli O157*, and *Campylobacter* infections in humans in the U.S. originate from food of animal origin.

3. The use of antimicrobials in animals will cause resistance to develop, and there is a potential that resistant *Salmonella, E. coli*, and *Campylobacter* will be transferred to humans through food.

Status of Antimicrobials

CVM has approved new antimicrobials for use in animals for therapeutic purposes as prescription-only products for several years. This prescription-only policy is based on CVM's desire to assure the proper use of antimicrobials through precise diagnosis and correct treatment of disease to minimize animal suffering and to avoid unsafe residues. Antimicrobial products for use in animals must meet stringent standards for safety, efficacy, and quality to be approved.

Safety in food-producing animals includes extensive evaluation of data to ensure that residues in food derived from treated animals are safe for human consumption. In the past, microbiological safety studies which examined resistance patterns and pathogen load were only required for antimicrobials to be used in feed for more than 14 days.

Due to concerns about antimicrobial resistance, the safety assessment now must include evaluation of resistance concerns with the conduct of pre-approval studies and post-approval monitoring programs (PAMPs). These requirements may be waived for antimicrobials of low public health concern. Details of the post-approval programs will vary on a product-specific basis.

The data generated by the PAMP will allow the CVM to take action after approval of antimicrobial drugs to mitigate the development of resistance, including as a last resort, withdrawal of the product from the market. Product-specific PAMPs will be used to supplement data collected through the National Antimicrobial Resistance Monitoring System created in the U.S. in January 1996. This program is a collaboration among FDA, CDC, and USDA and monitors shifts in antimicrobial susceptibilities of 17 antimicrobial drugs in zoonotic enteric organisms from both veterinary and human sources.

Prudent Use

CVM believes it is critical that prudent use of antimicrobials be emphasized to minimize the development of antimicrobial resistance and to ensure the continued efficacy and availability of antimicrobial products for use in food-producing animals. CVM defines “Prudent Use” of therapeutic antimicrobial agents as the…

> “Use that maximizes therapeutic effect while minimizing the development of resistance.”

On May 6, 1998, CVM and CDC jointly sponsored a meeting of veterinary practitioners, human health specialists, epidemiologists, and representatives of livestock producer groups to launch a discussion of prudent use of antimicrobials. The discussion will now be continued by the veterinary community, which is expected to develop the prudent use principles.

Those attending the meeting agreed that the American Veterinary Medical Association (AVMA), which represents veterinary professionals, will lead efforts on prudent use. AVMA has formed a Prudent Use Steering Committee (SC), and provided operating money. Membership on the SC will include representation from CDC and CVM. CDC and CVM have also recommended that the AVMA add representation from the human medical community to the SC.

Future Regulation of Antimicrobial Products

CVM views as its **top priority** the need to define scientifically-based criteria and/or standards for the regulation of antimicrobial products. The Center expects that these efforts will help long-term to create a stable regulatory environment for these products.

The following are some of the issues on the regulation of antimicrobial products that will need to be addressed by CVM:

1. Does CVM have the necessary tools to remove from the market products that present a public health concern AFTER approval?

2. Should CVM use the same criteria for assessing safety for therapeutic and non-therapeutic products?

3. What criteria should be used to define whether a particular antimicrobial product will need to undergo pre-approval studies to evaluate resistance concerns and should have a post-approval monitoring component to continue this evaluation?

4. Is CVM's current definition of "therapeutic" appropriate for the current regulatory environment?

5. Should the establishment of withdrawal periods include evaluation of pathogen load and resistance patterns?

6. Are there additional research areas that need to be addressed?

FDA is currently working to establish criteria to address whether particular antimicrobial products will need to undergo pre-approval studies to evaluate resistance concerns and should have a post-approval monitoring component to continue this evaluation. The Agency anticipates holding a public meeting, possibly as early as this fall, to obtain public input about these criteria.

Approval of Quinolone Antibiotics

CVM's view is that approval of quinolone antibiotics for therapeutic use in animal agriculture is appropriate under the following conditions:

1. The product meets all FDA requirements for safety, efficacy, and quality.

2. A system is used to ensure that once approved, products are used in accordance with labeled indications and prudent use principles.

3. There is a monitoring system to track changes in resistance.

4. Corrective action, including product withdrawal as a last resort, can be taken if scientific evidence is presented post-approval which demonstrates continued use of the product may present a public health concern.

THOMPSON TO MANAGE CVM ANTIMICROBIAL RESISTANCE EFFORTS

Dr. Sharon R. Thompson, a Veterinary Medical Officer in FDA's Center for Veterinary Medicine (CVM), has been appointed to the newly created position of Associate Director for Veterinary Medical and International Affairs. In this capacity, Dr. Thompson will be responsible for managing and coordinating national and international activities on antimicrobial resistance related to drug therapy in food animals. She will lead CVM's efforts to develop an overall strategy to define scientifically-based standards for the regulation of antimicrobial products. She will also lead the Center's initiative to promote the prudent use of antimicrobials in food animals. Dr. Thompson will continue to provide direction to the Center's international activities. Dr. Thompson currently serves as FDA's representative to the Veterinary International Cooperation on Harmonization (VICH) Steering Committee.

Since 1992, Dr. Thompson has been a Special Assistant to the Center Director, concentrating in the area of international affairs. In her new role, she will work with experts, both within and outside the Agency, to address issues involving antimicrobial products for animals. She will serve as FDA's spokesperson and authoritative source of information and advice on matters related to this issue. Dr. Thompson will also serve as the official liaison to other government agencies and foreign and domestic organizations working in this area.

The previous article provides information about the Center's activities and concerns about the use of antimicrobial drugs in food animals. CVM views developing criteria or standards for regulating these products to address the emerging concerns about antimicrobial resistance as the Center's top priority. CVM expects that these efforts will help create a stable regulatory environment for these products.

Center Director Stephen Sundlof said, "I am very pleased that Dr. Thompson has agreed to take on this new role. Her experience in the international arena dealing with complex regulatory issues will be invaluable in helping CVM to formulate a consistent science-based strategy to address this important issue."

FDA APPROVES RESTRICTED USE OF CLENBUTEROL PRODUCT FOR HORSES

On May 11, 1998, the Food and Drug Administration (FDA) approved Ventipulmin® (clenbuterol hydrochloride) Syrup for use in horses affected with airway obstruction, such as occurs with Chronic Obstructive Pulmonary Disease (COPD) also known as the heaves. There are a large number of horses afflicted with this condition, and many

veterinarians, horse owners, and members of horse-related veterinary and owner associations have been eager to see this needed drug available in the U.S. for reducing pain and suffering in affected horses.

Ventipulmin Syrup is an orally administered product used to decrease the work of breathing in horses with obstructive airway disease. The product is available only by prescription, and the recommended duration of treatment is 30 days. The most notable side effects are sweating, muscle tremors, hives, restlessness, and increased heart rates. These subside within a few days after the initiation of treatment.

Ventipulmin Syrup contains a small amount of clenbuterol which belongs to the family of compounds called Beta-agonists. It is well known that clenbuterol affects lung and heart functions. In Europe, human illness was associated with consumption of meat containing clenbuterol residue. The most notable incident occurred in Spain in 1990 and was associated with consumption of liver from animals that had been illegally administered clenbuterol. Symptoms from ingestion of clenbuterol residues can include increased heart rate, muscular tremors, headache, dizziness, nausea, fever, and chills. Concerns over the abuse of clenbuterol in food animals in the U.S. have led to strict enforcement against illegal sales and use. FDA has added clenbuterol to the list of drugs that are prohibited from extra-label use in animals (Code of Federal Regulations, Title 21, Part 530.41), and FDA and USDA both use tests that can monitor for residues at slaughter.

The sponsor of Ventipulmin, Boehringer Ingleheim Animal Health, Inc. (BIAH), of St. Joseph, MO, is taking several steps to ensure that the approved drug is not misused. These include:

-- Instructing salespersons to notify practicing veterinarians that the use of this product in food animals is prohibited, and that veterinarians involved in such illegal activities will be held accountable.

-- Notifying salespersons and veterinarians that law enforcement agencies can test food animals for signs of exposure to clenbuterol.

-- Providing sales information on Ventipulmin to FDA, including names and addresses of purchasers, to enable FDA to track suspicious distribution patterns.

FDA believes that the controls BIAH has instituted will substantially assist the Agency prevent the illegal use of clenbuterol in food-producing animals.

FDA's approval of clenbuterol for use in horses is in concert with the conclusions of FDA's Veterinary Medicine Advisory Committee (VMAC). In a November 1993 meeting, the VMAC concluded that Ventipulmin offered no significant increased risk of diversion and misuse as compared to illicit sources of this drug, and that no extra

restrictions (beyond the existing post-approval monitoring and enforcement activities by FDA and the actions to be taken by the sponsor) should be applied to the distribution and sale of this product.

FDA believes that the drug can be used in compliance with its labeling to reduce pain and suffering in horses, and that adequate means are in use to safeguard the food supply from illegal residues.

PREVENTION OF BSE IN THE U.S. THROUGH FEED REGULATION

by John Honstead, D.V.M., M.S.

Introduction

Bovine spongiform encephalopathy (BSE) belongs to a group of poorly understood emerging diseases known as transmissible spongiform encephalopathies (TSE's), and presents a unique regulatory challenge to FDA. In this article, I will briefly review information on transmissible spongiform encephalopathies, describe the UK BSE epidemic and review the U.S. FDA BSE regulation and the scientific basis for the requirements.

Characteristics of TSE Diseases

TSE's are fatal diseases of humans and a number of animal species, primarily ruminants. They are progressively degenerative central nervous system (CNS) diseases that are characterized by a long incubation period, a shorter clinical course of neurological signs, and 100-percent death rate. Animal TSE's include sheep scrapie, BSE, transmissible mink encephalopathy, feline spongiform encephalopathy, and chronic wasting disease of deer and elk. TSE's in humans include Creutzfeldt-Jakob disease, Gerstmann-Straussler-Scheinker syndrome, kuru, and fatal familial insomnia. In the United States, naturally occurring TSE's of animals have been reported in sheep, goats, mink, elk, and deer. Recent evidence has shown a strong association between BSE and the occurrence of a new form of CJD (new variant CJD).

Because of their structure and mode of replication, the TSE agents do not seem to provoke an antibody response in the host. Therefore, detecting their presence by serological techniques or preparing protective vaccines may be difficult. However, post-mortem histopathology of brain tissue from animals with TSE's reveals bilaterally symmetrical degenerative changes in gray matter and neuronal vacuolation.

The cause of TSE's is unknown. Proposed causes of TSE's are the infectious protein or prion theory, an unconventional virus, and Spiroplasma, among others. Resistance of the agents to physical and chemical agents that destroy nucleic acid have essentially ruled out conventional microbiological agents as the cause. Thus the prion theory seems to be the most likely explanation. The mode of transmission of the TSE's is also not understood. As a measure of infectivity, laboratory animals are

innoculated with TSE tissue, generally through intracerebral injections, and observed for signs of disease.

Bovine Spongiform Encephalopathy

BSE is a TSE of cattle with a prolonged incubation period following oral exposure (2-8 years). BSE was first recognized as a distinct disease of cattle by researchers of the British Ministry of Agriculture, Fisheries, and Foods (MAFF) at Weybridge, England in November 1986. There were indications that the first clinical case of BSE may have been observed as early as April 1985.

The clinical signs of BSE include behavioral, gait and postural abnormalities, and usually begin with apprehension, increased reaction to sound and touch, a swaying gait, sometimes with high stepping, and kicking in the milking parlor. This is accompanied by subtle changes in the normal behavior of the cow such as a change in the milking order, separation from the rest of the herd while at pasture, disorientation, staring, and excessive licking of the nose or flanks. The disease progresses with stumbling, falling and eventually inability to stand. It ends with coma, seizures and death.

BSE has not been detected in cattle in the United States. Intensive efforts are in place both to determine whether the disease exists in the United States and to prevent its entry, e.g., USDA surveillance, by prohibiting the importation of BSE-infected cattle or feed. There is, nevertheless, a small risk that the disease could occur in the United States as it has in a number of countries in addition to the United Kingdom (UK). Sheep scrapie exists in the United States, and TSE's have been diagnosed in several other animal species. In addition to the possibility of transmission from these species to cattle and the risk of inadvertent importation of BSE-infected cattle or feed, the prion theory suggests that BSE could occur spontaneously.

Creutzfeldt-Jakob Disease (CJD) in Humans

Sporadic Creutzfeldt-Jakob Disease is a TSE of humans with no known cause, and exists throughout the world with an annual incidence of approximately one case per million population. The average age is 56 years, and clinical symptoms start with changes in sleeping and eating patterns, and often include confusion, inappropriate behavior, and lack of coordination.

In April 1996, British scientists reported a previously undetected new variant of CJD (nvCJD) in young patients with symptoms different from sporadic CJD. All the cases had histopathologic evidence of the spongiform changes, but also formation of amyloid plaques not typically seen in sporadic CJD. Clinically, nvCJD begins with a psychiatric presentation, including depression, anxiety, nightmares and hallucinations followed by memory impairment with dementia in the late stages. The clinical course may last up to 2 years. The prion protein in the nvCJD brains is the same prion protein found in cattle

with BSE, leading UK scientists to state that exposure to the BSE agent is the most plausible explanation for these findings though the exact route of exposure is unknown. There are currently 26 cases of nvCJD in the UK, and one in France.

BSE epidemic in the UK

Since BSE was first diagnosed in the United Kingdom in December 1986, more than 170,000 cattle have contracted the disease. BSE has also been reported in native cattle in France, Switzerland, Netherlands, Belgium, Portugal, Luxemburg, the Republic of Ireland, and Northern Ireland.

Epidemiological studies have characterized the outbreak of BSE in the UK as an extended common source epidemic. Each case, therefore, has been a primary case due to exposure to a single common source of infection. Investigators have identified several major risk factors that apparently contributed to the emergence of the disease and the resultant epidemic in the UK. USDA identified the following risk factors for BSE in the UK:

1. large sheep population relative to the cattle population,
2. a large, uncontrolled, scrapie incidence rate,
3. the production of greaves, an incompletely processed intermediate product in the rendering process,
4. changes in rendering processes, like the reduced use of solvent extraction,
5. the feeding of significant amounts, up to 4 percent of the diet, of meat and bone meal to young dairy calves.

The only common factor in the cattle with BSE is that feed containing meat and bone meal was fed to the affected animals. Further epidemiological studies, including computer simulation of the epidemic in the United Kingdom, suggest that feed contaminated by a TSE agent was the cause of the disease. Two possible hypotheses as to the original source of this agent were consistent with the epidemiological findings -- that it was the agent of scrapie itself, or that it was a cattle-adapted strain of a scrapie-like agent.

In the UK, dead sheep, many of which may have died of scrapie and cattle with BSE, were picked up by "knackers" for rendering into animal feed. This material was partially rendered into "greaves" which contained large amounts of the scrapie/BSE agent, and was fed to dairy calves in large amounts. The spread of BSE appeared to be facilitated by the feeding of rendered BSE-infected cattle back to calves. Changes in rendering practices may have potentiated the agent's survival in meat and bone meal. BSE agent recycled from cows to calves until the ruminant-to-ruminant feeding ban in 1989.

Efforts to Control BSE in the UK

In an extensive research project, various rendering processes used in the European Union were tested for their ability to inactivate the BSE agent in 15 pilot scale facilities. BSE brains were mixed with intestine and bone to replicate raw materials. The variables were type of process (continuous or batch), time, temperature, atmosphere, amount of fat, and particle diameter. Meat and bone meal was produced from each of the processes, and suspensions were assayed in inbred mice for infectivity. Four of the 15 processes produced meat and bone meal with detectable BSE. These processes were banned for use in the European Community (EC) member countries.

Regulatory controls taken to manage the BSE epidemic and minimize public health risks in the UK and other countries include an action to make the disease reportable (June 1988); a ban on the feeding of ruminant-derived protein supplements to other ruminants (July 1988); compulsory slaughter of suspect cattle (August 1988); and a ban on the feeding of the specified offals or their products to all pet and farm animals (September 1990). The UK has a Specified Bovine Materials (SBM) ban which prevents the whole head, spleen, tonsil, intestinal tract, spinal cord and lymph nodes from use in animal feeds or human foods, cosmetics, drugs or medicinal products. Additionally, the UK has a Heads of Sheep and Goat ban that prevents the use of sheep and goat heads for human consumption and requires them to be treated as SBM. The regulations in the UK are enforced by government inspections of slaughter and rendering plants, SBM collection centers, and incinerators; and by testing of feeds using an ELISA test to detect mammalian protein.

FDA BSE Regulation for U.S. Feeds

The FDA was requested by various customers and organized groups to take actions in the U.S. that ranged from no regulation at all to a complete stoppage of any animal protein recycling to animals. The most obvious question FDA had to face was: Why is a feed regulation necessary for the U.S. if there is no BSE? Even though BSE has not been diagnosed in cattle in the U.S., information and theories on TSE diseases raise concern that BSE could occur. If BSE does occur, the causative agent could be transmitted and amplified through feeding of certain processed animal proteins to cattle resulting in an epidemic. The greatest risk for cattle, given the prolonged incubation period of 2 to 8 years, would be unrecognized amplification in the cattle population, resulting in greater animal exposure. The announcement of the possible link between new variant-CJD and BSE, and new information about the origin and ecology of the BSE agent has caused increased concern about BSE regulation in the U.S.

The next question was: why not ban all animal proteins from the diets of U.S. animals? FDA's answer is that processed animal proteins have been safely fed to animals for many years before the BSE outbreak, and except for BSE, we are not aware of data indicating this practice is not safe. Therefore, the FDA rule utilized scientific data regarding the difference between animals with TSE's and animals with

no natural TSE, mammalian tissues with no TSE agent contained in them or processing that reduces the BSE threat. The FDA BSE rule reduces the threat of undetected amplification of BSE by banning mammalian tissues known to be a TSE risk from ruminant feed, but allows feeding of safe tissues.

Materials Affected by the Ban

The FDA BSE regulation prohibits the use of protein derived from mammalian tissue, with some exemptions, in feed for ruminant animals. The basis for the inclusion of only protein in the regulation is that only protein portions from TSE-affected animals have been capable of transmitting the disease to other animals. The regulation applies only to mammalian proteins because studies have not detected a TSE of plants or non-mammalian animals.

The exemptions are pure swine or pure equine proteins, blood and blood products, milk and milk products, gelatin and plate waste. Plate waste is defined as inspected meat products which have been cooked and offered for human food and further heat processed for feed. The term "prohibited materials" will be used to describe non-exempt mammalian proteins, and "non-prohibited materials" to mean all other proteins.

The scientific basis for exemption of **pure swine or pure equine proteins** is that these species have never been found to have a naturally-occurring TSE. We are aware that one pig out of ten, inoculated with BSE developed TSE lesions. We do not believe that this represents an event that occurs naturally in pigs. Pigs were no doubt exposed quite routinely in UK during the BSE epidemic before the feed bans, and no pigs came down with a TSE.

Blood and blood products, milk and milk products, and gelatin were exempt for the reason that none of these tissues have not been shown scientifically to play a role in transmitting BSE. The WHO considers all of these tissues to be of no risk for BSE based on scientific information.

The exemption for **plate waste** was proposed by the operations utilizing this as a feed source. They presented the case that meat is a low risk material for BSE, plate waste contains a small proportion of meat (2%) and high moisture requiring addition of 50 to 60% corn or soybeans for extrusion of animal feed. The initial cooking for human use would reduce the amount of any TSE agent present and the second heating and high pressure for animal feed often at 290^0 to 400^0 F would reduce it even more.

Industries Affected

Renderers, protein blenders, feed manufacturers, distributors including haulers, and individuals that are responsible for feeding ruminants are directly affected in this regulation. The BSE regulation covers mammalian protein materials from renderer to

the animal feeder including all the operations between. The scientific rationale for this goes back to the MAFF calf study demonstrating that one gram of BSE brain fed one time to calves will cause them to get BSE. The minimum dose to transmit BSE orally in bovines is therefore believed to be less than 1 gram.

The entry of prohibited mammalian proteins into **rendering establishments** is the first point of control for this regulation. Renderers are defined as anyone that processes slaughter byproducts, animals unfit for human consumption or meat scraps. This includes traditional renderers, renderers that blend animal protein products, those who collect slaughter byproducts and minimally process them, and those who collect and distribute slaughter byproducts to firms other than renderers.

Renderers can either separate or not separate prohibited and nonprohibited materials. All prohibited materials must be labeled "**Do not feed to cattle or other ruminants**", records such as invoices or similar documents must be maintained to track the materials through their business, made available to FDA for copying and inspection and kept for 1 year. Renderers that separate prohibited and nonprohibited material must label the prohibited material, maintain records, obtain nonprohibited material from single species slaughter facilities, and provide for measures to avoid commingling or cross-contamination of prohibited and nonprohibited materials.

There are many businesses that handle mammalian proteins between renderers and animal feeders including **protein blenders, feed manufacturers, and distributors including haulers**. These processors and haulers can either separate or not separate prohibited and nonprohibited materials. All prohibited materials must be labeled "Do not feed to cattle or other ruminants", records maintained to track the materials through their business, made available to FDA for copying and inspection and kept for 1 year. Protein blenders, feed manufacturers, distributors including haulers that separate prohibited and nonprohibited material must label the prohibited material, maintain records, obtain nonprohibited material from single species slaughter facilities, and provide for measures to avoid commingling or cross-contamination of prohibited and nonprohibited materials.

In order for the regulation to be fully effective, **individuals and establishments that are responsible for feeding ruminants** must ultimately handle prohibited feed properly, and be held accountable. They must maintain all feed invoices and copies of labels for feeds that contain animal protein, make them available to FDA for copying and inspection and keep records for one year.

Pet foods were exempted from the regulation because once manufactured and packaged for sale as pet foods, they are unlikely to be fed to ruminants. Once pet food is damaged or otherwise unfit for pet use, the material must be handled according to the regulation like any other mammalian protein since it can be diverted to ruminant feed.

Role of Processing

Processing cannot assure complete removal of BSE agent from feed materials as demonstrated by research in rendering. When this is coupled with the fact that very small amounts of BSE agent can cause disease orally in cattle, a dilemma arises in a BSE-free country that utilizes rendered ruminants for ruminant feeds. It becomes apparent that processing alone cannot be counted on to stop undetected amplification if BSE occurred undiagnosed at any time in the future. Processing must be combined with controls over source materials for ruminant diets to assure complete safety from BSE.

Production of animal feeds involves several physical processes such as heat and pressure applied over time. When sufficient heat and pressure are applied to BSE-infected materials for a sufficient time, a decrease in infective titer is seen as measured by bioassay in susceptible mice. When the conditions are very severe, the final product may not have any detectable infectivity remaining. The safety of the final materials is complicated by the lack of confidence in the mouse bioassay coupled with the fact that very small amounts of the prion agent can cause disease.

The Role of Feed Testing

A provision of the FDA feed regulation provides for exemption from certain requirements if the feed is tested for BSE agent using an FDA-validated test. To date, no such test exists, but this provision may stimulate research and development in the future.

The UK is presently using an ELISA test for ruminant proteins to enforce its mammalian-to-farm animal feeding ban. FDA is reviewing a polymerase chain reaction test developed in Italy for consideration as a regulatory tool. It is currently focused on the identification of bovine DNA, but may be able to be modified to identify mammalian material. In the future, test information may be used to focus inspectional efforts relative to the exemptions.

Impact of FDA BSE Regulation

The ultimate impact of the regulation will be a reformulation of ruminant feeds to exclude prohibited materials, and labeling of non-ruminant feeds that contain prohibited materials to prevent undetected amplification of BSE in the U.S. There has been a small decline in the price of mixed-mammalian meat and bone meal. Many inquiries have been received by FDA from the feed and animal feeding industries regarding the requirements and methods for complying, indicating a genuine concern for compliance.

Conclusion

Although the risk of BSE in the U.S. is small, the consequences and cost would be very high, should it be detected. U.S. cattle would be at risk for disease, and the human population could be at risk for nvCJD. The FDA BSE regulation identifies and isolates prohibited mammalian proteins from the renderer through processing and transportation, and prohibits their feeding to ruminants. The provisions and requirements of the regulation are based on current science. Because BSE is an emerging disease, the scientific base is limited, and should be expanded through research.

REGULATION OF MEDICATED FREE-CHOICE FEEDS FOR PASTURE CATTLE
by Daniel. A. Benz, Ph.D., P.A.S.

Under the authority of the Federal Food, Drug, and Cosmetic Act, as implemented in the Code of Federal Regulations (21 CFR 510.455), the Center for Veterinary Medicine (CVM) approves the use of medicated free-choice supplemental feeds to provide both therapeutic and performance-enhancing new animal drugs to pasture cattle. The following new animal drugs are approved for use in medicated free-choice supplemental feeds: bambermycins (Gainpro®), chlortetracycline (Aureomycin®), fenbendazole (Safe-Guard®), lasalocid (Bovatec®), monensin (Rumensin®), and poloxalene (Bloat Guard®). Their conditions and levels of use are found in 21 CFR 558 (New Animal Drugs for Use in Animal Feeds).

The free-choice administration of new animal drugs in feeds involves feeds that are placed in feeding or grazing areas and are not intended to be consumed fully at a single feeding or to constitute the entire diet of the animal. Such methods of administering drugs include, but are not limited to, medicated blocks (agglomerated feed compressed or rendered into a solid mass and cohesive enough to hold its form), mineral mixes, and liquid feed tank supplements ("lick tank" supplements) containing one or more new animal drugs. Each medicated free-choice supplemental feed contains a variety of nutritional ingredients and has a unique formulation. These drug containing free-choice supplemental feeds are manufactured at local feed mills from Type A medicated articles (the drug containing premixes) and contain some form of supplemental nutrition. Over 300 feed mills, of which many are small family-owned and operated businesses, produce approximately 100,000 tons of medicated free-choice supplemental feeds annually that are fed to over 19.5 million cattle. The free-choice method is the most practical and economical means to deliver drugs to pasture cattle, since these animals are often seen on an infrequent basis.

Medicated free-choice feeds are unique drug dosage forms in that they are available continuously to the animals in both dry and liquid forms, and therefore, must be formulated to both entice and restrict intake in order to provide the drug within a safe and effective range. Feed composition (i.e., levels of salt, molasses, minerals or protein), physical form, and in some cases, drug content, regulate consumption and consequently dosage of a drug. Inherent to this free-choice concept is the probability of under- or over-consumption, as well as sporadic intake patterns of such variation

that effectiveness will not be realized. Over-consumption of these drug-containing supplemental feeds may also result in animal toxicosis and/or unsafe residues in human food. Thus, free-choice feed systems represent one of the greatest potentials for drug overdosing which could result in animal safety hazards or human food safety residue concerns.

In 1984, representatives of the drug industry petitioned CVM contending that regulation of medicated free-choice feeds containing previously approved drugs using the same stringent requirements and criteria used for unapproved new animal drugs was excessive and unwarranted. As a result, CVM reevaluated the requirements, agreed with the petitioners, and published new innovative guidelines (Guidelines for Evaluation of Effectiveness of New Animal Drugs for Use in Free-Choice Feeds, January 1985). Although less stringent than former requirements, these new guidelines still required substantial evidence that a particular feed would be consumed in an amount and with such frequency that a safe and effective dose of the drug would be received.

Using a universal effectiveness database (a database describing the underlying effectiveness of the new animal drug in a free-choice environment) which was developed by one drug sponsor, and the coefficient of variation statistic, CVM has developed and implemented an innovative comparative approach to demonstrate efficacy for this drug in numerous formulations of free-choice supplemental feeds. This method permits the feed manufacturer to collect only intake pattern data for their product which is then compared with the intake pattern associated with the effectiveness data in the universal database. The rationale was that if eaten in like amounts with comparable patterns of intake, the drug would be safe and effective regardless of formula variations of nutritional and carrier elements. The impact of this approach is to reduce the burden (e.g., decreased use of experimental resources) on the feed manufacturer, while still maintaining a safe and effective product.

In addition to use of the comparative technique with coefficients of variation with universal databases, another method was implemented that allowed the application sponsor to collect both drug intake and effectiveness in one, two, or three studies and make these intake coefficients of variation comparisons within their own data. Overall, these innovative approaches, which were fully accepted and supported by CVM and industry scientists, facilitate the approval of dozens of drug-bearing free-choice feed formulations with maximum efficiency at minimum cost to the small business community. Availability of these free-choice feeds allows livestock producers to increase productivity and to continue to provide a safe food supply.

Once several medicated free-choice supplemental feeds were approved, a new problem surfaced when feed manufacturers needed to change ingredients in their approved formulation(s). This unanticipated problem arose because each ingredient has the potential to affect palatability of the free-choice supplemental feed as well as drug intake, and, consequently, impact the safety of the human food supply. Inclusion

or exclusion of ingredients in the free-choice supplemental feed formulation by feed mills is dictated by nutritional attributes of the ingredient and least costing of the formulation, which is standard operating procedure in the feed industry to remain competitive. Through the effective use of its nutritional and physiological expertise, CVM has predicted the impact of the requested changes on palatability and drug intake. Consequently, CVM was able to permit feed manufacturers to make minor adjustments in their approved formulation and facilitate the use of least cost formulation by expert
evaluation of each individual request. In most cases, the requested change was permitted after scientific review by CVM, and feed manufacturers were able to continue to provide the medicated free-choice feed to their customers without delay or further costly studies, and without jeopardizing the human food supply.

In summary, CVM approves the use of medicated free-choice supplemental feeds to provide both therapeutic and performance-enhancing new animal drugs to pasture cattle through several approaches. The impact is to reduce the regulatory burden on industry, while maintaining safe and effective medicated free-choice products, that are both practical and economical to deliver new animal drugs to pasture cattle.

The author was CVM's 1997 nominee for the FDA Excellence in Review Science Award.

CVM VETERINARIAN COLLABORATES WITH COLOMBIAN AGRICULTURAL OFFICIALS

Dr. Thomas Letonja, a reviewer with CVM's Division of Therapeutic Drugs for Food Animals was invited to collaborate in the planning and drafting of a project for the strengthening of the Veterinary Services in the Ministry of Agriculture and Rural Development of Colombia. This organization is responsible for the registration, surveillance and control of veterinary drugs marketed in the country. The project is financed by the Inter-American Development Bank. This initiative is in response to several international activities on globalization of regulatory veterinary medicine sponsored by the International Office of Epizooties (OIE). The goals are to work toward a greater harmonization of regulations and standards in the international trade of veterinary drugs and biologics.

Agriculture and livestock activities represent the most important economic area in the country, generating approximately 35% of the exports from Colombia. In the year 2000 it is expected that Colombia will be declared free of Foot-and-Mouth Disease, which will allow the country to offer livestock products to the world market.

The main objective of the project is the improvement of the National System of Agriculture and Livestock Protection including surveillance, inspections of pharmaceutical facilities, residue monitoring, and controls.

The registration and evaluation of veterinary drugs and biologics is the responsibility of the Instituto Colombiano Agropecuario, ICA (Colombian Institute of Agriculture and Livestock). The Institute includes a team of 16 professionals and several consultants from Universities and other government organizations. The regulatory activities of the reviewers are complemented by a Laboratory that conducts chemical, physico-chemical and microbiological analysis of veterinary drugs and biologics, both on imported and domestic samples.

Dr. Letonja met with several government officials and professionals to obtain the necessary background information on the structure of the Ministry of Agriculture and Rural Development and functions of the units involved in the approval of veterinary drugs. He also presented a seminar on the approval process of animal drugs in FDA/CVM. The presentation was well attended by staff professionals and was followed by an active discussion on specific topics of the presentation. In addition, Dr. Letonja participated in meetings with officials of the Ministry of Health to discuss the status on meat (including seafood), milk and eggs regulatory activities, in particular, the sampling of meat in the slaughterhouses for the detection of veterinary drug residues.

Dr. Letonja prepared a report of his evaluation of the current situation of the drug approval process and provided recommendations for strengthening the activities of the Instituto Colombiano Agropecuario to achieve their goals in animal and human safety.

The government of Colombia is very interested in establishing a continuous consulting agreement with FDA/CVM, with special emphasis on the drug approval process and the human food safety of residues of veterinary drugs. The harmonization of the requirements in both countries would ensure the human food safety of all animal products exported to the United States and other countries.

EXPIRATION DATES FOR PROGRAM® EXTENDED

FDA has approved two supplemental new animal drug applications (NADAs) for Lufeneron (Program®). On February 7, 1997, FDA approved a supplemental NADA for Program® Suspension which extended the expiration date on the product for one additional year (to 36 months). Also, on September 19, 1997, FDA approved a supplemental new NADA for Program® Tablets which extended the expiration date on that product for one additional year (to 48 months). FDA based these approvals on supporting stability data submitted by the sponsor of the drugs, Novartis Animal Health.

FDA is responsible for approving original, supplemental, and abbreviated new animal drug applications under the Federal Food, Drug, and Cosmetic Act (the Act). The Act requires that new animal drugs be shown to be safe and effective for their intended uses. It also requires that the methods, facilities, and controls used for the manufacturing, processing, and packaging of the drugs be shown to be adequate to preserve their identity, strength, quality, and purity.

The Code of Federal Regulations (Title 21, Part 514.1) specifies the proper form and information required to be submitted by drug sponsors. One of the requirements of these regulations is that drug sponsors submit data from stability studies that substantiate the request for a specific expiration date and provide information on the stability of the drug product.

CORRECTION

In the last issue of the FDA Veterinarian, it was reported that Dr. Robert Holland who has just been appointed to the FDA's Veterinary Medicine Advisory Committee, "...is currently the Animal Drug Coordinator for the North Central IR-4 Program, a project designed to facilitate approval of drugs for minor species." Dr. Holland is actually the Animal Drug Coordinator for the North Central Region for the National Research Support Project #7 (NRSP-7). The program was originally part of the Interregional Project Number 4 (IR-4) for clearance of compounds to control diseases and pests of both plants and animals. In 1993, a separate project, NRSP-7, for minor use animal drug approval was established by the USDA. This program has generated data supporting the approval of 20 new animal drugs for minor species and at any given time has between 20 and 30 active projects in progress. To learn more about NRSP-7, visit the website at http://bluehen.ags.udel.edu/nrsp7.html, or contact the FDA liaison to the program, Dr. Meg Oeller at (301) 594-1650.

FDA GUIDANCE FOR NON-REGISTERED FEED MANUFACTURERS AVAILABLE

by Karen A. Kandra

FDA's Center for Veterinary Medicine (CVM) has released a revised guide intended to help manufacturers of medicated feed that are not required to register with the FDA comply with the Current Good Manufacturing Practice (CGMP) regulations, 21 CFR 225.120 - 225.202.

The revised guide is titled "Guidance for Industry -- GMP's for Medicated Feed Manufacturers Not Required to Register and Be Licensed with FDA" (Guidance Document 72). It is a revised version of the 1989 publication "GMPs for Medicated Feed Manufacturers Not Required to Register with FDA."

The Animal Drug Availability Act (ADAA) of 1996 established feed mill licensing as a replacement for FDA's previous medicated feed application (MFA) system. Those manufacturers that are exempted from registration and licensing include those that manufacture only Type B or Type C medicated feeds using: (1) Category I drugs as Type A medicated articles or Type B or C medicated feed, and/or (2) Category II drugs as Type B or C medicated feed.

The CGMPs were established to provide guidance for medicated feed manufacturers to assure that their products meet the identity, strength and quality

which they should possess with respect to their drug content. These regulations apply equally to all manufacturers of medicated feeds with more stringent regulations for licensed facilities and a less stringent set for facilities that are not required to be licensed by FDA. This guide is designed to provide information and answer typical questions about the regulatory responsibilities for those feed manufacturers that are not licensed and registered with FDA.

The guide is available through the CVM Internet Home Page **(http://www.fda.gov/cvm)** or by contacting the FDA Veterinarian at 301-594-1755. Additional information regarding this document may be obtained by contacting CVM's Division of Animal Feeds, Dr. George Graber, 7500 Standish Place, HFV-220, Rockville, MD 20855, 301-827-6651.

The following questions and answers are taken from the revised guide.

BASIC INFORMATION

Q. Who must comply with "Current Good Manufacturing Practices?"

A. All manufacturers of medicated feed must follow CGMPs. Anyone producing an animal feed containing an animal drug is subject to this requirement. This includes large multi-plant manufacturers and single-plant manufacturers, as well as on-farm mixing operations.

Q. What is the legal basis for requiring compliance with CGMPs?

A. The Federal Food, Drug, and Cosmetic Act (the Act) Section 501 (a)(2)(B) states that a medicated feed containing an animal drug is adulterated if not produced in conformance with CGMPs. Adulterated feeds and manufacturers of adulterated feed are subject to regulatory action.

Q. Does the term "medicated feed" mean only a complete feed, one that can be fed as the sole ration?

A. The term "medicated feed" includes all medicated feed products intended to be a substantial source of nutrients in the diet of an animal. It includes products commonly referred to as supplements, concentrates, premix feeds, and base mixes. It is not limited to complete feeds intended to be the sole ration of the animal.

Q. Where are the CGMPs described?

A. Regulations describing CGMPs have been published by FDA in the Code of Federal Regulations (CFR), Part 225. There are two sections of these regulations -- one for mills registered with FDA to use drug sources requiring

approved medicated feed mill licenses, and one for mills using only drug sources which do not require such licenses and registration with FDA. These questions and answers address the non-registered, non-licensed mill CGMP regulations.

Q. How does following the CGMPs benefit me as a manufacturer of medicated feed?

A. Observance of CGMPs should result in medicated animal feeds that meet product specifications. This will help assure that meat, milk, and eggs produced with these feeds contain no violative drug residues. Non-compliance with the CGMPs carries the potential of medicated feed products which could cause harm to consuming animals or result in unsafe drug residues in the edible products from these animals.

OPERATIVE TERMS

Q. What drug products used in medicated feeds are covered by CGMPs?

A. All animal feeds containing animal drugs (medications) are covered by CGMPs.

Q. Are all animal feed drugs regulated the same with respect to CGMPs?

A. No. The applicable CGMP Requirements are based on the categorization of the drug and the potency. All drugs are placed into one of two categories based on whether or not there is a withdrawal requirement at the lowest continuous feeding level and the potential for harmful effect from misuse of the drug.

Q. What are the two categories of drugs?

A. The two categories of drugs are known as “Category I” and “Category II.”

Category I consists of those drugs for which no withdrawal period is required at the lowest continuous feeding level for any approved species. Category I drugs do not require an approved Medicated Feed Mill License for manufacturing of medicated feeds unless they are combined with a Category II drug source requiring a Medicated Feed Mill License.

Category II consists of drugs that either require a withdrawal period at the lowest feeding level in at least one species for which the drug is approved, or are regulated on a “no-residue” basis because of a carcinogenic concern. Higher potency sources (Type A products) of Category II drugs require a Medicated Feed Mill License to manufacture medicated feeds. Lower potency sources (Type B products) are subject to the same requirements as Category I drugs.

Q. What are the medicated product types?

A. There are three (3) medicated product types: Type A, Type B, and Type C. These terms replace "medicated premix, concentrate, supplement, and complete feed," which are no longer being used in FDA's regulations. The Type A product is considered a drug, and the Type B and C products are medicated feeds. A Type A medicated article is a product that consists of one or more new animal drugs intended for use in the manufacture of a medicated feed. It is the subject of an approved new animal drug application. A Type B medicated feed is intended solely for the manufacture of other medicated feeds (Type B or Type C). A Type C medicated feed is a complete feed for the animal, or is a feed that may be fed "top-dressed" or offered "free-choice" in conjunction with other animal feed.

REGISTRATION

Q. What feed manufacturing establishments must register with FDA?

A. Any feed manufacturing establishment that uses one or more Type A sources of Category II drugs to manufacture medicated feeds must register with FDA as a medicated feed establishment. Registration is not required if drug use is limited to Category I drugs (all types) and Type B sources of Category II drugs--that is, no Medicated Feed Mill License is held.

Q. Where can I find information on the procedures for registration if I desire to register and obtain a Medicated Feed Mill License?

A. Procedures for registration can be obtained from a local FDA office or you can write to the Drug Listing Branch (HFD-334), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, Maryland 20857.

Q. What about producers who mix their own feed?

A. All manufacturers of medicated feeds are subject to the same rules. If firms (commercial mills, feedlots, producers, mobile mixers, etc.) use only Category I products and/or Category II Type B drug products, registration with FDA is not required. These manufacturers must comply with the medicated feed CGMPs in 21 CFR Parts 225.120 to 225.202 (the less detailed set of CGMPs). They are not subject to biennial inspection by FDA.

If a firm uses one or more Category II Type A medicated articles as drug sources, it must register with FDA and comply with the medicated feed CGMPs in 21 CFR Parts 225.10 to 225.115 (the more detailed set of CGMPs). As a registered establishment, it is subject to inspection by FDA or FDA-

commissioned State inspectors at least once every two years for compliance with these CGMPs.

INSPECTIONS

Q. When are feed manufacturers inspected?

A. All registered feed manufacturers are subject to at least one inspection during each two-year period. This inspection requirement is waived for manufacturers not required to register.

Q. Will my feed manufacturing operation be inspected if it is not required to be registered?

A. There will be no routine FDA biennial inspection. The fact that a feed manufacturing operation is not registered, however, does not mean that it is totally exempt from Federal inspection. An FDA investigator or an FDA-commissioned State inspector may conduct an inspection to confirm registration status of the firm or to follow up on a report of a drug residue, or for other appropriate reasons. Also, your State feed control office may conduct routine inspections to determine compliance of your facility with the less detailed CGMPs.

Q. How can I, as a non-registered feed manufacturer, avoid problems?

A. By knowing the CGMP regulations and by self-inspecting your own establishment, you can determine if your operation complies with the spirit and intent of the regulations. Non-compliance may result in product adulteration and unacceptable risks to animal and/or public health. Ensure that all employees involved in the manufacture of medicated feeds have an understanding of the manufacturing and control operation(s) which they perform, including the location and proper use of equipment, and that all necessary procedures and controls are in place and followed.

Q. What should I look for when I inspect my own feed manufacturing operation?

A. Self-inspections of non-registered feed manufacturers should cover at least the following areas:

A. Facilities and Equipment

- *225.120 Buildings and grounds*: Is there adequate space for equipment, and processing and storage of medicated feeds? Does construction maintenance minimize vermin and pest infestation?

- *225.130 Equipment*: Is equipment capable of producing a medicated feed of intended potency and integrity? Are adequate cleanout procedures used to avoid unsafe contamination of medicated and non-medicated feeds? Such procedures may include physical cleanout, flushing, sequencing of production, and similar actions. Are scales and metering devices accurate and suitable for their intended purposes?

- *225.135 Work and Storage Areas*: Are work areas, drug storage, and equipment free of pesticides, fertilizers and other toxic substances that could contaminate feeds?

B. Product Quality Assurance

- *225.142 Components*: Have adequate procedures been established and maintained for the identification, storage and inventory control of all drug sources intended for use in the manufacturing of medicated feeds? Are the procedures and records adequate to permit detection of incorrect use?

- *225.158 Laboratory Assays*: Have necessary corrective actions been determined and taken when laboratory assays of drug components indicated a medicated feed was not within permissible limits? Are these records kept for at least one year?

- *225.165 Equipment Cleanout Procedures*: Have adequate procedures been established to prevent unsafe contamination of feeds? Are they followed?

C. Labeling

- *225.180 Labeling*: Are labels received, handled and stored in a manner that ensures correct labeling and prevents mix-ups? Are all medicated feeds adequately labeled?

D. Records

- *225.202 Records*: Are written records kept containing the formula, date of mixing, and date of shipment (if not for own use)? Can you locate and recall product if this is necessary?

ENFORCEMENT

Q. What will happen if my operation fails a CGMP inspection?

A. The objective of FDA regulatory programs is to encourage and assure medicated feeds are properly manufactured and labeled. Enforcement activities include actions to correct and prevent violations, remove violative products or goods from the market, and punish offenders. Enforcement efforts range from a letter notifying the individual or firm of a violation and requesting correction, to seizure of product, to criminal prosecution of the individual or firm. The type of action recommended for failure to follow CGMPs will depend upon the nature of the violation and the public health concern, FDA policy, previous history of violations by the firm, and other factors. Your State may have a similar range of enforcement efforts under its authority.

FOOD ADDITIVE PETITIONS FILED

In the May 12, 1998, Federal Register, FDA announced that Alltech Biotechnology Center has filed a petition (FAP 2238) proposing that the food additive regulations be amended to provide for the safe use of selenium yeast as a source of selenium in animal feeds. Additional information is included in the Federal Register and from Dr. Nelson S. Chou, Center for Veterinary Medicine (HFV-228), Rockville, MD 20855, (301) 827-0161.

In the May 12, 1998, Federal Register, FDA announced that Vanetta S.p.A. has filed a petition (FAP 2239) proposing that the food additive regulations be amended to allow the use of menadione nicotinamide bisulfite in swine diets as a source of vitamin K activity and niacin. Additional information is included in the Federal Register and from Dr. Michaela G. Alewynse, Center for Veterinary Medicine (HFV-228), Rockville, MD 20855, 240-453-6848.

PUBLICATIONS

NRC Publishes Swine Nutrition Requirements

The Subcommittee on Swine Nutrition, Committee on Animal Nutrition, Board on Agriculture of the National Research Council (NRC), has published the Nutrient Requirements of Swine, Tenth Revised Edition, 1998. This publication contains a reassessment of the nutrient requirements of swine and incorporates new information that was used to establish the requirements. A better understanding of the nutrient requirements and nutrient sources allows one to accurately formulate diets to meet the pig's dietary requirements without producing overages of nutrients that are excreted into the environment. A major change was made in this edition in that the subcommittee provided the biological basis used to establish energy and amino acid requirements in the form of integrated mathematical equations (models). A computer program and software allow the user to create tables of nutrient requirements for swine of a specific body weight and level of productivity.

Copies of Nutrient Requirements of Swine are available for purchase from the National Academy Press, 2101 Constitution Avenue, NW, Lockbox 285, Washington, DC 20055. Credit card orders may be placed by calling 1-800-624-6242 or 202-334-3313 in the Washington, DC metropolitan area; Internet, http://www.nap.edu/bookstore.

FINAL DEADLINE FOR RELABELING OF CTC/OTC FEEDS

In an April 1, 1997 CVM UPDATE, the Center for Veterinary Medicine announced that it was extending the time for relabeling of some Type A medicated articles containing chlortetracycline (CTC) and oxytetracycline (OTC) to provide for an orderly transition in the marketplace. In that release, CVM stated that the Center was granting an extension of time to feed manufacturers using these Type A products to allow for development and printing of new labels and depletion of existing labeling for products made from the Type A articles until **April 1, 1998**. This deadline has now been reached.

Feed manufacturers may no longer use Type A medicated articles that are not labeled in compliance with the findings of the National Academy of Sciences/National Research Council (NAS/NRC), Drug Efficacy Study Group's (DESI) effectiveness evaluations and the approval of "me-too" NADAs that were dependent upon the DESI-finalization. Also, feed manufacturers may not distribute feeds that are not labeled in conformance with the DESI changes.

Products affected by this change include:

Product	Sponsor	NADA Number
Chlortetracycline Type A Medicated Articles	Hoffmann La Roche, Inc.	NADA 48-761 NADA 100-901
	Pfizer, Inc. NADA 92-286	and NADA 92-287
	ALPHARMA (formerly A.L. Labs.)	NADA 46-699
	ADM Animal Health & Nutrition Division (formerly Feed Specialties Co.)	NADA 48-480
	PennField Oil Co.	NADA 138-935

Permitted Indications

Chickens, Turkeys, Swine, Sheep, Calves, Beef and Non-Lactating Dairy Cattle. For improved production efficiency, and for control and treatment of various bacterial diseases susceptible to chlortetracycline (CTC.)

Product	Sponsor	NADA Number
Oxytetracycline Type A Medicated Articles	Pfizer, Inc.	NADA 8-804 NADA 95-143
	PennField Oil Co.	NADA 138-938

Permitted Indications

Chickens; Turkeys; Swine; Sheep; Calves, including veal calves; Beef and Non-Lactating Dairy Cattle, Bees, Fish, and Lobsters. For increased rate of weight gain, improved feed efficiency, and control and treatment of various bacterial diseases susceptible to oxytetracycline (OTC).

Questions concerning the DESI evaluations and NADA approvals should be directed to Dr. Dianne McRae, FDA/Center for Veterinary Medicine, 7500 Standish Place, HFV-102, Rockville, MD 20855. Questions about labeling and compliance should be directed to Ms. Gloria Dunnavan, FDA/Center for Veterinary Medicine, 7500 Standish Place, HFV-230,

VETERINARIAN INDICTED IN CLENBUTEROL SMUGGLING CASE

On May 22, 1998, a Federal grand jury indicted Dr. Jerry M. Bonham, a veterinarian from Cordell, Oklahoma, on charges of conspiring to buy illegal clenbuterol that had been smuggled into the U.S. from Canada. Dr. Bonham owns the Bonham Cattle Company and the Cordell Animal Hospital in Cordell, Oklahoma. The indictment charges that between 1988 and 1994, Dr. Bonham purchased more than $68,000 worth of smuggled clenbuterol, knowing that the drug was not approved for use in the U.S.

The indictment charges Dr. Bonham with conspiring with Dr. John Phillip Murray, a veterinarian in Oxbow, Saskatchewan, Canada, and others, to violate Federal laws prohibiting the sale of smuggled merchandise and introducing adulterated drugs into interstate commerce. Dr. Murray was convicted by the U.S. in 1995 for his role in smuggling clenbuterol into the United States. In addition, the Professional Conduct Committee of the Saskatchewan Veterinary Medical Association (SVMA) found Dr. Murray guilty of professional misconduct, and in 1997 suspended his veterinary license for 2 years, followed by 3 years of practice under the supervision of a veterinarian licensed and in good standing with SVMA. In addition, SVMA fined him $30,000 plus court costs in excess of $50,000.

Clenbuterol, which belongs to the family of compounds called Beta-agonists, has never been approved for use in food animals in the U.S. In Europe, human illness was associated with consumption of meat containing clenbuterol residue. Symptoms from ingesting clenbuterol-contaminated meat can include increased heart rate, muscular

tremors, headache, dizziness, nausea, fever, and chills. Concerns over the abuse of clenbuterol in food animals in the U.S. have led to strict enforcement against illegal sales and use.

Recently, FDA approved Ventipulmin® Syrup, which contains a small amount of clenbuterol, as a restricted use prescription-only drug for treating horses affected with airway obstruction. When FDA approved Ventipulmin®, several controls were put in place to ensure that this drug would not be misused in food-producing animals.

The charges against Dr. Bonham are the result of an investigation by agents of the FDA's Office of Criminal Investigations and the U.S. Customs Service. The case is being prosecuted by attorneys from the U.S. Attorney's Office for the Western District of Oklahoma and the U.S. Justice Department's Office of Consumer Litigation.

An indictment is merely an allegation that a person has committed an offense. All persons charged are presumed innocent unless and until found guilty by a judge or jury.

If convicted, Dr. Bonham faces a maximum penalty of five years in prison and a fine of up to $250,000 on the charge.

REGULATORY ACTIVITIES

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

- Daniel Wright, Wright Dairy Management, Inc., Payson, UT
- Corrie Vanderham, C&R Vanderham Dairy, Mira Loma, CA
- George L. Zemak, Zemak Farms, Savona, NY
- Jose Pereira, Pereira Dairy, Winton, CA
- Maria Machado, President, Machado Wilton Corporation, Wilton, CA
- William Bryan Hargett, Greenville Livestock, Inc., Ayden, NC
- Victor Camacho, Victor Camacho Cattle, Tulare, CA
- Gerald Morris, Rancho Provimi, Stockton, CA
- Mike A. Kuckenbaker, Riverdale, CA

These violations involved illegal residues of penicillin in cows, streptomycin in a cow, sulfadimethoxine in a cow, penicillin and sulfadimethoxine in cows, gentamicin in a cow, penicillin in pigs, and gentamicin in calves.

Warning letters were also sent to the following firms/individuals which had a history of offering animals for sale for human food use which were adulterated with drug residues. These warning letters stated that these individuals/firms had offered animals for slaughter that contained illegal drug residues:

- John Zonneveld, Zonneveld Dairies, Inc., Laton, CA
- Marcelino R. Amaral, Jr., Marcelino Amaral and Sons Dairy, Stevinson, CA
- Cornell Kasbergen, Rancho Teresita, Tulare, CA

These violations involved illegal residues of penicillin in a dairy cow, sulfadimethoxine in a cull dairy cow, and gentamicin in a cull dairy cow.

Warning letters were sent to the following firms/individuals for violations from GMPs:

- Clemence A. Fischer, Fischer's Mills, Inc., Princeton, WI
- Kevin Kruse, O.H. Kruse Grain & Milling, Pixley, CA
- Dean Issacson, Western Consolidated Cooperative, Sunburg, MN
- Craig Willardson, Nulaid Foods, Inc., Ripon, CA
- Lee L. Krienke, Sleepy Eye, MN
- Warren Gerdes, Farmers Coop Elevator Company, Buffalo Lake, MN

A warning letter was sent to Don Van, General Manager, EQyss International, Inc., Vista, CA, for marketing several products which are new animal drugs which are not the subject of approved New Animal Drug Applications (NADAs).

Harry Cleberg, Chief Executive Officer of Farmland Industries, Kansas City, MO, received a warning letter because Mr. Charles L. Groom, Swine Production Specialist for Farmland Industries, regularly visits two contract hog growing operations in Cylinder, IA, and recommends the use of various drugs (including prescription drugs) to improve the health of the animals. Mr. Groom is not a veterinarian and has recommended several drugs not approved for use in swine.

A warning letter was also sent to Dr. Steven P. Slagle, Animal Medical Center, Inc., Algona, IA, who provides veterinary services for the two Farmland Industries' contract hog growing operations in Cylinder, IA. The warning letter states that Dr. Slagle deviated from regulations governing extralabel drug use in animals and failed to establish controls to assure that prescription veterinary drugs are sold only upon written or other order of a licensed veterinarian based upon a valid veterinarian/client/patient relationship. FDA's investigation determined that Dr. Slagle supplied drugs recommended by Mr. Charles L. Groom (who is not a veterinarian) upon request from the hog growers.

NEW ANIMAL DRUG APPROVALS

Company

Pharmacia & Upjohn Co. (NADA 141-077)

Generic and (Brand) Names

Spectinomycin Solution (Adspec™ Sterile Solution) Rx

Indications

Cattle. For treatment of bovine respiratory disease associated with Pasteurella haemolytica, P. multocida, and Haemophilus somnus.

Routes/Remarks

SUBCUTANEOUS: The NADA provides a tolerance for spectinomycin residues in cattle kidney and in cattle muscle. The acceptable daily intake(ADI) for total residues of spectinomycin is also codified. Apply as follows: Injection in the neck. Not more than 50 ml at each site. Not to be slaughtered within 11 days of treatment or used in female dairy cattle 20 months of age or older. Not for use in veal calves.
Federal Register 5/1/98.

Abbott Laboratories (NADA 141-098)	Propofol emulsion (PropoFlo®) Rx	Dogs. For induction of anesthesia, maintenance of anesthesia, or induction of anesthesia where maintenance is provided by inhalation anesthetic.	INTRAVENOUS. Federal Register 5/4/98.

BioScience Division of Milk Specialties (NADA 141-101)	Competitive exclusion cultures, Lyophilized bacterial cultures (Preempt™)	Chickens. For the early establishment of intestinal microflora in chickens to reduce salmonella colonization.	TOPICAL in water spray mist: Administer at less than one day old. Do not administer antibiotics to treated chickens. Federal Register 5/7/98.
Novartis Animal Health US, Inc. (NADA 141-105)	Lufenuron (Program™) Rx	Cats. For control of flea populations.	SUBCUTANEOUS: 10 mg per kilogram body weight every 6 months.

Do not use in dogs.
Federal Register 6/1/98.

ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Med-Pharmex, Inc. (ANADA 200-235)	Neomycin sulfate soluble powder	Cattle (excluding veal calves), swine, sheep, goats. For treatment and control of bacterial enteritis caused by Escherichia coli susceptible to neomycin sulfate.	DRENCH or IN DRINKING WATER: ANADA is a generic copy of Upjohn's NADA 11-315. Federal Register 4/9/98.
Marsam Pharmaceuticals, Inc. (ANADA 200-187)	Isoflurane Rx		

Horses and dogs. As an inhalant for induction and maintenance of general anesthesia.

INHALANT: ANADA 200-187 is a generic copy of Ohmeda Pharmaceutical Products Div., Inc.'s NADA 135-773, AErrane®. Federal Register 5/1/98.

Phoenix Scientific, Inc. (ANADA 200-230)

Guaifenesin Injection Rx

Horses. For use as a skeletal muscle relaxant.

INTRAVENOUS: ANADA 200-230is a generic copy of Summit Hill Laboratories' NADA 48-854 (Gecolate Injection). Federal Register 5/29/98.

SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Hoechst Roussel Vet (NADA 141-034)	Bambermycins (Flavomycin®)	Pasture cattle (slaughter, stocker, and feeder). For increased rate of weight gain.	MEDICATED FEED: The firm filed the application to provide for using a 10-grams per pound bambermycin Type A article to make a free-choice Type C feed providing 10 to 20 milligrams per head per day. Not intended for use in breeding animals. Federal Register 4/16/98.
Elanco Animal Health (NADA 38-878)	Monensin	Chickens, Turkeys, and	

Quail. To revise specifications for monensin bulk drug substance used to make a Type A medicated article.

MEDICATED FEED: The firm filed the application to provide revised assay information used in checking the specification of the monensin bulk drug substance.
Federal Register 5/4/98.

Elanco Animal Health
((NADA 95-735)

Monensin

Cattle and Goats. To revise specifications for monensin bulk drug substance used to make a Type A medicated article.

MEDICATED FEED: The firm filed the application to provide revised assay information used in checking the specification of the monensin bulk drug substance.
Federal Register 5/4/98.

Schering-Plough Animal Health Corp. (NADA 141-063)	Florfenicol (Nuflor® Injectable Solution) Rx	Cattle. For treatment of bovine respiratory disease.
		INTRAMUSCULAR: The firm filed a supplemental NADA providing for a revised warning against use of the product in veal calves. Federal Register 5/15/98.
Novartis Animal Health US, Inc. (NADA 140-915)	Milbemycin Oxime (Interceptor® FlavorTabs®) Rx	Cats. For the prevention of heartworm disease and removal of roundworm and hookworms.

ORAL: The supplemental NADA provides for expanding the initial indications to include separate dosage and labeling for use in cats 6 weeks of age or greater and 1.5 pounds of body weight or greater. Federal Register 5/29/98.

Captions

Graphic B --

Photo by Karen A. Kandra

Graphic C --

Photo by Karen A. Kandra