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Center for Veterinary Medicine
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Company, Owner Fined, Placed on Probation for Selling Misbranded Animal Drugs

A Federal court in Iowa in December 2004 fined Livestock Concepts, Inc., and its owner, Becky Rus, and placed the company and the owner on probation for selling prescription animal drugs without a veterinarian's oversight, and in some cases with false or forged documents.

The company was caught because cattle treated with drugs the company sold tested positive for illegal drug residues. The positive findings triggered an investigation.

Rus was given a year's probation and fined $25,000, ordered to pay $50,000 in restitution to the Food and Drug Administration's (FDA) Office of Criminal Investigation, and as part of a plea agreement required to forfeit $225,000 to the U.S. government.

Her company was also sentenced to a year's probation and ordered not to sell prescription drugs during that time. In addition, the company was fined $25,000 and ordered to pay $400 in special assessments.

The investigation was carried out by FDA's Kansas City District Office, Office of Criminal Investigations, and Center for Veterinary Medicine.

The investigation was started after the U.S. Department of Agriculture's Food Safety and Inspection Service detected illegal levels of drug residues in slaughtered cattle. Whenever USDA discovers illegal residues, it contacts FDA to conduct an investigation into the reasons for the residues.

In this case, the investigator reviewed the records of the livestock producer whose animals were found with illegal residues. During this review, the investigator also checked with the veterinarian used by the producer and found that the veterinarian-client-patient relationship was not correctly in place.

This investigation, which took place in 2002, found that Rus on behalf of Livestock Concepts continued to purchase and dispense prescription drugs without a veterinarian's prescription. The investigation found that from March 1999 to April 2000 the company did not employ any veterinarian, but continue to buy and dispense prescription drugs. As a result, Rus was in violation of Federal law by selling misbranded drugs.

Livestock Concepts provided false and forged documents to drug suppliers in order to continue to buy prescription drugs. The documents said a veterinarian was working for Livestock Concepts, even though the company was not employing one. The forged documents allowed the company to continue to buy prescription drugs that it dispensed.

The company used another veterinarian who sold drugs through the company even though he never examined the animals to be treated, which under Federal law is considered selling misbranded drugs.

Investigators also found that Livestock Concepts shipped veterinary drugs to a customer in Virginia based on a prescription form prepared and signed by a registered pharmacist, not a veterinarian. In addition, the company shipped animal drugs to a customer based on a prescription from a doctor of osteopathy. In another case, a veterinarian signed a prescription a month after the drugs were shipped.

Not unique case

This case is not unique, according to Kansas City District Office investigators. Each time a case of illegal drug sales is uncovered, FDA takes action. Often that action is an injunction and seizure of the product. But, when evidence is strong, local investigators can refer the case to FDA's Office of Criminal Investigations. The U.S. Attorney then can decide if the case should be brought to court.

FDA is not likely to take action against the veterinarians, doctors, or pharmacists who aided Livestock Concepts in illegal drug sales, but FDA will notify States of any suspected illegal activities. States often take action against individuals.

Livestock producers who knowingly buy and use veterinary drugs illegally

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In This Issue

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

Second Feed Safety System Meeting Focuses on Framework, Risk Ranking Model

The team headed by Center for Veterinary Medicine (CVM) that is developing the Animal Feed Safety System (AFSS) has developed a draft framework to describe the features it believes should make up the feed system, and that framework was the focus of CVM's second public AFSS meeting, that was held April 5-6, in Omaha, NE.

The docket for this meeting will remain open after the meeting, but the AFSS team intends to steadily move ahead.

Written comments should be sent to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to *http://frwebgate.access.gpo.gov/cgi-bin/leaving.cgi?from=leavingFR.html&log=linklog&to=http://www.fda.gov/dockets/ecomments*.

In the draft framework, published in February 2005, the AFSS team identified four components that will make up the feed safety system, explained the purpose and goals for each of the components, and identified gaps within each of them.

In the draft framework, published in February 2005, the AFSS team identified four components that will make up the feed safety system, explained the purpose and goals for each of the components, and identified gaps within each of them.

CVM's goal under AFSS is to create a nationwide, comprehensive, risk-based system for regulating feed. The AFSS plan will describe how feeds can be manufactured, distributed, and used in a way that minimizes risks to animals and humans, particularly the risks from food derived from animals.

The AFSS team is made up of officials from CVM, from the Food and Drug Administration's (FDA) Office of Regulatory Affairs and Office of the Commissioner, and State officials.

CVM held its first public meeting on AFSS in September 2003. At that meeting, CVM officials described the system they were hoping to create and asked for public comment about the plans. CVM collected comments during and after the meeting, using them to develop definitions for the principles of "comprehensive" and "risk-based," and create a list of elements essential for process control under a feed safety system. The list of seven feed safety system elements, published in March 2004, covers the entire process of feed production and transportation.

Framework

For the next public step in developing the AFSS, the team created the draft framework, which was the focus of the April meeting. The framework reflects the comments received about the AFSS.

The draft framework separates the AFSS into four components that cover all aspects of feed production.

- ***Component 1: Ingredients and the Approval Process.*** The purpose of

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Company, Owner Fined, Placed on Probation for Selling... *(Continued)*

can also face an injunction or prosecution following an FDA investigation. The U.S. Department of Agriculture can also place sanctions on the livestock producer. The best way for livestock producers to avoid problems is to work closely with their veterinarians when selecting and using animal drugs, the Kansas City FDA officials said.

While not required by law, drug suppliers could consider notifying FDA if they see drugs they supply being used under suspicious circumstances, the investigators said.

Improper use of veterinary drugs in animals that produce food will lead to residues, as in the Livestock Concepts case. Residues can be harmful to consumers who eat food products made from the treated animals. Improper use of antimicrobials can contribute to the problem of antimicrobial resistant bacteria. And improper drug use can harm the health of the animals being treated.

FDA VETERINARIAN

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VICH Meeting Scheduled for May 25-27 in Washington, DC

The third International Cooperation on Harmonisation of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH) Conference is scheduled for May 25 – 27, 2005, in Washington, DC.

It will be hosted by the U.S. delegation, which includes the Food and Drug Administration (FDA), the U.S. Department of Agriculture's Animal and Plant Health Inspection Service, and the Animal Health Institute, which represents the animal health industry.

VICH is an international program aimed at harmonizing the technical requirements for the registration or licensing of veterinary medicinal products. VICH was officially launched by regulatory and veterinary medicine industry officials representing Japan, the European Union, and the United States in April 1996.

The "VICH3" conference will focus on the numerous VICH guidelines that have been published in draft or final form during the last three years and will mark the closure of the first phase of the harmonization of regulatory requirements among the VICH participating regions.

Conference presenters will discuss the results of the VICH Expert Working Groups, including those on ecotoxicity, biologicals quality monitoring, quality, safety, pharmacovigilance, antimicrobial resistance, and target animal safety. Members of the public will be able to comment on the VICH activities at this meeting.

VICH3 participants will also discuss the VICH strategy for future achievements in 2006-2010.

Dr. Lester Crawford, FDA Acting Commissioner, will open the conference, and keynote speaker Dr. Pedro Lichtinger, President of Pfizer Animal Health, will address the industry perspective on global trends in veterinary medicine.

More information about the program can be found at *www.fda.gov/cvm/index/vich/VICH_Conference_Program.pdf*.

Second Feed Safety System Meeting... *(Continued)*

this component of the feed safety system requires that all ingredients used in feed are safe. This component also describes the mechanisms FDA and CVM use to make sure all ingredients and additives used in feed are safe for the uses intended. The principal mechanism is the Federal Food, Drug, and Cosmetic Act.

However, FDA has also relied on the Association of American Feed Control Officials to define ingredients. The gap identified under AFSS for this component is that a non-Federal organization is used to list ingredients and provide information. The framework document identifies the use of an FDA Compliance Policy Guide to correct the gap.

- ***Component 2: Limits for Animal Feed Contaminants.*** The purpose of this component is to identify the hazards that feed might contain and set limits to those hazards. Also, this component calls for developing test methods to find the hazards.

  One gap the AFSS team identified is the lack of a ranking process that would allow FDA to determine which hazards require limits and analytical methods. CVM is developing a risk assessment method, which was also discussed at the meeting. More information about the risk ranking system is presented later in this article.

- ***Component 3: Process Control for the Production of Safety Feed.*** This component deals with proper manufacture, packaging, storage, and distribution of feed ingredients and mixed feed to keep hazards out.

  FDA has regulations covering medicated feed. However, under AFSS, FDA and CVM might need a broader regulatory approach to cover production, packaging, storage, distribution, and use of feed ingredients and non-medicated feeds.

- ***Component 4: Regulatory Oversight.*** This part of the feed safety system calls for regulators to apply a risk-based system so that FDA can use resources for the greatest benefit in terms of keeping feed safe.

  A gap that the framework identified is that some segments of the feed industry, including transporters and on-farm mixers, are outside the normal regulatory scope of FDA and the States.

Risk ranking

Because AFSS will be a risk-based system, CVM is developing a risk-ranking method that can be used to identify and determine the relative levels of risks from contaminants in feed.

Karen Ekelman with CVM's Division of Animal Feeds explained that AFSS will focus on actual risks to humans and animals from feed. She added that a risk is the likelihood of harm from a hazard, and the likelihood is based both on the significance of the hazard and the possibility an animal or human will be exposed to that hazard. Risk equals hazard times exposure, she said.

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Ask CVM

Q: What are the rules concerning the use of color additives in animal feeds and pet foods?

The 1960 Color Additives Amendment brought all colors, natural and synthetic, under the Federal Food, Drug, and Cosmetic Act. Regulatory responsibility was given to the FDA's Center for Food Safety & Applied Nutrition (CFSAN). Under this amendment and the color additives regulations, the term "foods" includes foods intended for animals.

Since the FDA's Center for Veterinary Medicine (CVM) has responsibility for ensuring that animal feed products are safe and accurately labeled, CFSAN consults with CVM when a color additive is proposed for use in animal feed products.

In addition, when a color additive is proposed for use in a meat, poultry, or egg product, its safety, technical function, and conditions of use must also be evaluated by the Labeling and Compounds Review Division of the U.S. Department of Agriculture's Food Safety and Inspection Service, as provided in the Federal Meat Inspection Act, the Poultry Products Inspection Act, the Egg Products Inspection Act, and related regulations.

CVM's role in approving colors for use in animal feeds

CFSAN receives and processes color additive petitions (CAP) from firms seeking to use new color additives in animal feeds. A copy of the petition is sent to CVM for consulting review, usually within 90 days. After reviewing a combination of laboratory and field trials, CVM makes recommendations regarding safety of the product under the conditions of intended use. CVM comments on only the target animal safety section of the petition. CFSAN reviews the other sections including manufacturing chemistry, human food safety, efficacy, and environmental safety.

Prior to submitting the petition, upon CFSAN suggestion, the petitioner may contact CVM directly for advice on how to design, conduct, and report on target animal safety studies. CVM has not developed specific guidelines for evaluating the safety of color additives to the target species; thus, CVM follows the principles established in 21 CFR 570 and 571 for evaluating the safety of food additives intended for animals. For example, each target animal safety study must be accompanied by a statement that the study was conducted in compliance with the FDA's Good Laboratory Practice (GLP) regulations to ensure that proper procedures were followed during the design, conduct, and reporting of the study.

If the target animal safety information is found acceptable, a memo is issued to CFSAN advising that CVM has no additional questions regarding the safety of the product to the target species under the conditions of intended use. If the information is found to be unsatisfactory, a memo is issued to CFSAN advising that the target animal safety section of the petition is incomplete. The CVM memo specifies what additional information is needed.

When the color additive is found to be safe under the conditions of intended use, CFSAN seeks CVM concurrence on the draft regulation and final product label.

Labeling feed products containing color additives

The labeling format recommended by the Association of American Feed Control Officials (AAFCO) in its Official Publication is used to ensure that adequate labeling is provided. In addition, the feed products containing color additives should conform to the label-

(Continued, next page)

Second Feed Safety System Meeting... *(Continued)*

Decisions based on hazard alone typically overemphasize frightening or unusual hazards, but underemphasize common or familiar hazards, Dr. Ekelman said. In addition, a system focusing on hazards must require that the hazards be eliminated, which is not a practical approach for a feed system, she said.

The AFSS that CVM wants to create will allow FDA to quantify the actual risk reduction, or, in other words, quantify the benefit from actions. Dr. Ekelman said that a risk-based system will permit FDA to balance regulatory resources against the relative risks of feed hazards.

FDA has identified 175 feed contamination hazards, including biological, chemical, and physical. The relative risk of these contaminants will be assessed using the AFSS risk ranking method.

Each feed hazard gets a consequence "score," which ranks the danger of each hazard. For instance, a hazard that could cause a death would be assigned a greater score than a hazard that would cause slight injury.

The hazards are then given exposure scores under the risk model. If animals are not likely to be exposed to a particular hazard in feed, the hazard would get a lower score than one to which many more animals would be exposed.

The risk ranking method also adjusts for the potentially modifying or enhancing effects to the hazards from the feed manufacturing process.

FDA will use the risk ranking method to determine which feed contaminants present the greatest relative risks to animal or human health, and then to decide how to best eliminate, reduce, or control the risks.

Ask CVM *(Continued)*

ing requirements specified in Part 70.25 of the 21 CFR, i.e., all color additives shall be labeled with sufficient information to assure their safe use and to allow a determination of compliance with any limitations imposed by the color additive regulations. Further, the presence of the color additive in finished feed should be declared in accordance with Part 501.22 of the 21 CFR, i.e., among other things, the feed label must contain a statement of artificial coloring. The presence of the color additive in the animal product (e.g., fish) that has been fed feeds containing the additive shall be declared in accordance with Sections 101.22(k)(2) and 101.100(a)(2) of the 21 CFR.

Certifiable colors

The Nutrition Labeling and Education Act of 1990 (NLEA) amended section 403(i) of the Federal Food, Drug and Cosmetic Act to require that a certifiable color additive used in food must be listed in the ingredient statement by its common or usual name (e.g., Blue 2, Red 40), and not by generic terms such as "artificial colorings." All labels printed after July 1, 1991, must comply with this requirement. However, color additives exempt from certification can still be declared generically.

While this provision of the Act applies both to human food and animal feed, there are no regulations pertaining to animal feeds. Therefore, the "old" regulations still apply to animal feed and pet foods at this time. Colors may be declared as "artificial color," "artificial coloring" or by their common or usual names in the ingredient list. However, use of the common or usual name alone does not negate the requirement under 21 CFR 501.22 to declare the presence of an artificial color in the product, whether the color is certified or not. Thus, an ingredient statement listing titanium dioxide, caramel, beta-carotene or other substance whose intended use is to impart color to the food must be further identified as a color in the ingredient list, unless the presence of an artificial color is conspicuously declared elsewhere on the label. Examples would be "caramel color," or "colored with titanium dioxide."

Color additives used in animal feeds

CVM has used regulatory discretion and has permitted all color additives approved for use in human foods under Part 73-Subpart A (Foods), Part 74-Subpart A (Foods) and Part 82-Subpart B (foods, drugs, and cosmetics) of the 21 CFR to be used in animal feeds. That is, it is unlikely that CVM would take regulatory action against their use in animal feeds, provided that they are used as color additives in accordance with the regulations, and used at levels consistent with good manufacturing practice. In addition, there are color additives approved for specific uses in animal feeds.

The primary reasons for adding colors to feeds are to impart color to the feed itself and to impart color to animal products, such as meat, skin, and eggs.

The primary reasons for adding colors to feeds are to impart color to the feed itself and to impart color to animal products, such as meat, skin, and eggs. With regard to pet food, the reasons manufacturers add colors to these products are similar to the ones for human food, i.e., in most cases, colors are added to meet consumer expectations.

Imparting color to feed

Additives intended to impart color to feeds are added for feed identification purposes. For example, during the feed manufacturing process, a marker (color) is added to a selenium premix to identify that a manufactured feed contains selenium. A feed manufacturer may also use color to identify a feed that contains a certain animal drug.

Additives used to impart color to animal feeds are the same ones listed for use in human foods, i.e., the ones listed under sections 73, 74, 82 of the 21 CFR. For the purpose of imparting color to animal feeds, there are two color additives specifically approved: ultramarine blue, which colors salt intended for animal feed, and synthetic iron oxide, which is intended to color dog and cat foods.

Labeling claims

If the manufacturer of a color additive intends to claim that, in addition to impart color to animal products, it performs other technical functions such as increase rate of weight gain, increase the rate of egg production, and/or improve feed efficiency, such color additive is regarded by CVM as an animal drug. Thus, to be used in animal feed, such product needs to be approved both as a color additive by CFSAN and as an animal drug by CVM.

We note that there are animal drugs, e.g., Roxarsone (21 CFR 558.530), that were approved for uses such as increased rate of weight gain, improved feed efficiency, and improved pigmentation. Color additive approval was not required for the "improve pigmentation" claim, because these products contain no colorants and they are not intended to add color to the skin of the bird. By improving the animal health and skin appearance, they improve the pigmentation already present in the skin, which makes the product more appealing to the consumer.

Adverse reaction reports

Many customers and pet nutritionists believe that, among other ingredients, the presence of artificial colorings can cause problems such as allergic reactions. However, according with CVM's Division of Surveillance, no adverse reactions have been reported that could be traced back to a color additive present in an animal feed product.

CVM Researchers Use Latest Science to Develop Methods for Detecting Animal Drug Residues

by Richard L. Arkin

Along with its responsibility to be sure that drugs are safe when they go on the market, the Food and Drug Administration (FDA) also has responsibility to be sure drugs are used safely. FDA's Center for Veterinary Medicine (CVM) has found that the latest developments in science and refinements in lab equipment significantly help in that effort.

Improper use of drugs in animals may leave residues in animal-derived edible tissues that could be hazardous to consumers. CVM is responsible for assuring that significant residues of drugs that have been used to treat the animals are not present in human foods such as milk or other dairy products that come from animals or in tissues that become human food after slaughter, such as meat from swine and cattle.

Drug tolerance, withdrawal times

CVM and the U.S. Department of Agriculture's Food Safety Inspection Service (FSIS) participate jointly in a program to monitor the use of animal drugs, identify improper use, and protect the nation's food supply from violative drug residues that can pose a potential health threat.

To ensure food safety, FDA sets a tolerance level for drugs used in food-producing animals. A tolerance is a level at which a substance may be present in a food that the Agency has determined is consistent with safety when the food is consumed by humans.

The tolerances that FDA establishes include a safety factor to assure that the drug will have no harmful effects on the human consumers of the food product. To do so, the Agency determines the level at which a drug does not produce any measurable effect in laboratory animals, then determines acceptable daily intake levels for humans, withdrawal times (the period necessary after administration of the drug to an animal for the animal's metabolism to clear the drug so that any residue in meat or milk will be below the tolerance level), and drug tolerance so that the concentration of drug residues in edible tissues or milk will be below the acceptable daily intake level for humans when they are consumed. These tolerance levels are then used for monitoring, surveillance, and research.

In meat, seafoods, poultry, and milk, unsafe drug residues may result from a number of circumstances, such as illegal use of a drug in a food-producing animal, extralabel drug use in such an animal (permitted by law in certain circumstances) if excessive dosages have been administered, or if insufficient time has passed between administration and slaughter or harvest for the drug to clear the animal's system.

A corporate or individual cattle farmer who repeatedly presents animals adulterated with illegal drug residues for slaughter creates a significant health risk to consumers, so investigating repeat violators is a top priority for FDA.

A growing need for fast, efficient test methods

The need for fast and efficient test methods has become greater since the enactment of the Animal Medicinal Drug Use Clarification Act, which allows for extralabel use of animal drugs by veterinarians under certain conditions. Occasionally, this can mean the presence of a drug residue when one might not ordinarily be expected.

The need for more efficient test methods has also become clearer with the increased availability of imported food products. The use of drugs in food-producing animals overseas has been increasing, giving rise to the potential that import products may contain residues of drugs not permitted for use in food-producing animals in the United States. Another concern is the potential use in food-producing animals of human drugs not approved for veterinary use, unapproved new animal drugs, or other substances.

FDA's role focuses primarily on the protection of the food supply. For this purpose, test methods to determine whether harmful materials, such as drug residues, are present in the food supply are used both for initial screening tests in the field and in the more rigorous analysis that takes place in the laboratory.

Historically, field test methods have involved use of portable "test kits" in which chemical, bacteriological, or immunoassay assays are used. On-the-spot test results are made available through easily readable visual signals, such as color changes. These field tests have generally been effective as rough screening tests to detect the presence of a drug residue or family of residues, but generally have not provided much analytical detail by which a specific drug residue can be identified or quantified.

Fortunately, more informative in-laboratory residue methods can provide this specificity. Over the past

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CVM Researchers Use Latest Science... *(Cont.)*

15 years there have been dramatic improvements in technology for combining liquid chromatography (LC) and mass spectrometry (MS). These improved techniques enable rapid, sensitive analysis of antibiotics and other veterinary drugs. Modern LC/MS techniques have largely supplanted older technologies for analyzing trace levels of bioactive compounds of the type regulated by CVM.

The challenge has been to apply these new techniques to analyze the complex and varied components of foodstuffs and veterinary samples.

CVM's Office of Research has long been involved in studies to validate analytical methods. In the last several years, however, as new interfaces between LC and MS have moved from the experimental stage, through expensive scientific research, to less expensive commonly used techniques, the Office of Research has focused on refining this science and broadening its uses. Office of Research scientists have accepted the cutting-edge challenge of adapting newly available science into practical test methods that can analyze the multiple components of the molecules in foodstuffs and veterinary samples.

Test method development

The Division of Residue Chemistry in the Office of Research is charged with the development of test methodologies to address CVM's post-market surveillance needs for analytical methods for drug residues in animal-derived foods. Drug sponsors are responsible for developing methods for new animal drugs, but normally these are single-compound methods. CVM has become involved in researching multi-compound test methods, which are more efficient and have more widespread applicability. A sample preparation for a multiple-compound test may be as time-consuming as one for a single-compound test, but in a multiple-compound test, only one sample preparation is required. Similarly, there are higher initial equipment costs and higher costs for training analysts to use the equipment for multiple-compound tests, but the time saved in running a single test operation instead of many separate ones should bring overall costs down. The result is greater efficiency that should bring real-world cost savings as they become widely adopted.

Regulatory methods that can detect and measure a broad range of drugs and other substances at very low concentrations, yet are rugged, fast, economical, and safe, are valuable to both FDA and FSIS. These would involve, ideally, minimizing sample preparation to the extent possible through use of more sensitive separation and detection technologies .

Liquid chromatography/mass spectrometry (LC/MS, see sidebar) has become an attractive and practical approach for the Office of Research to determine the presence and concentration of residues as LC/MS equipment has dropped in price and techniques have become more refined. In particular, LC/MS/MS (LC/tandem mass spectrometry) offers a high degree of specificity, extremely good sensitivity, potential for high throughput, and applicability to many compounds, giving it the ability to analyze multiple residues in a single procedure.

Multi-residue methods

Multi-residue methods are designed to look at one or several classes of compounds in a single analysis. Current single drug methods are often long, tedious, and provide only minimal information from an analysis. In the past decade, technological improvements have reduced the size of LC/MS/MS equipment so that it can fit on a laboratory bench, and improvements in personal computers have made it possible to link a bench-top LC/MS/MS set-up to a small PC. By utilizing improvements over the past decade in existing mass spectrometry and chromatography technology, practical laboratory methods can be developed that screen for many compounds in a single analysis.

Similarly, the Division of Residue Chemistry has been engaged in developing techniques to apply this science to the surveillance of multiple classes of drug residues in human foods. The first studies involved eggs and milk. Later studies have included meat, seafood, and honey. Some of the methods developed can identify up to three dozen compounds in a single extraction and analysis.

Methods to detect very low levels of banned drugs

Some veterinary drugs are potentially so dangerous that the FDA completely prohibits their use in food animals. Chloramphenicol and nitrofurans fall into this category.

When nitrofuran and chloramphenicol drug residues were first detected in export products from Southeast Asia to Europe, FDA had analytical methods for chloramphenicol, but they were not as sensitive as methods in use in the European Union with lower detection limits. In response, the Office of Research adapted and validated methods for these compounds to provide the Agency with improved regulatory analytical methods to better protect the U.S. food supply.

Using the new technology to detect residues

The Office of Research validates analytical methods used in FDA laboratories for compliance testing through a process known as a method trial.

A method trial establishes that a method performs as intended, that it is fit for its intended purpose, and

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CVM Researchers Use Latest Science... *(Cont.)*

that technology transfers successfully from laboratory to laboratory. This means that equipment is available and written procedures are developed that are clear, complete, and free of ambiguity so that the Agency and FSIS can use the methods with confidence.

It is only after a method is validated that the method can be considered to be acceptable for general use. Validated multi-residue methods allow both the Agency and industry to maximize resources by being able to screen for residues of several drugs in a single test process. The cost of the more sophisticated equipment and techniques can be more than balanced by the speed and efficiency of the multi-residue methods.

FDA chemist David N. Heller led the Office of Research team that developed two broad-scan analysis techniques for drug residues in eggs. One method can identify residues of 29 drugs, including tetracyclines, fluoroquinolones, and sulfonamides. Another can identify residues of nine other drugs, including ionophores and macrolides.

Methods developed by the Office of Research have begun to be used in surveillance of retail eggs in the United States. For example, surveillance has shown the occasional presence of the polyether ionophore, lasalocid, although at levels not considered to be a human health risk.

According to Heller, LC/MS/MS "opens a lot of doors" for techniques that "apply instrumental capabilities in new ways."

FSIS has also successfully implemented a procedure developed by an Office of Research team under the leadership of chemist Mary Carson, Ph.D., for identifying residues of nine aminoglycoside drugs, including gentamicin and neomycin, in cattle, swine, horse, chicken, and rabbit tissues. As a result, regulatory enforcement action has been expedited.

Another team under the leadership of Philip J. Kijak, Ph.D., and Hui Li, Ph.D., Office of Research chemists, has developed a multi-class method for 18 veterinary drugs in shrimp. The instrumental analysis time for screening 18 drugs in one sample is only about 19 minutes.

The Office of Research, FDA field laboratories, and the Florida Department of Agriculture and Consumer Affairs jointly validated methods for chloramphenicol in shrimp and crabmeat. The new methodology improved FDA's detection capability for this banned substance from 5 parts per billion to less than 0.3 parts per billion.

An LC/MS/MS method for determining and confirming residues of furazolidone, nitrofurazone, nitrofurantoin, and furaltadone in shrimp has been validated by a group led by Pak-Sin Chu, Ph.D., and is currently being adapted to other species, including channel catfish. The shrimp method has been transferred to FDA field labs that are responsible for analyzing imported seafood.

Michael H. Thomas, Division of Drug Chemistry Director, noted that the division's research was showing that the higher capital costs associated with LC/MS/MS multi-residue methods are likely to be outweighed by lower operational costs, because a single sample preparation and a single analysis process can take the place of separate preparation and traditional analyses.

Overall costs were being further reduced, he added, because "computer-based analysis has made LC/MS/MS more automated and more miniaturized." As a result, Thomas explained, "what had once been an esoteric research tool has now become commonplace."

(Related information follows in green background.)

Equipment Used by CVM in Methods for Residue Detection

The Center for Veterinary Medicine's Office of Research has added new technology as it becomes available. Here is a description of some of the equipment the researchers use for developing methods for detecting animal drug residues.

by Richard L. Arkin

Chromatography

Chromatography is a process by which a complex mixture is separated into its component compounds. Two principal types of chromatography are used at the Office of Research, Gas Chromatography (GC) and Liquid Chromatography (LC).

GC is used when the compounds are fairly volatile. Among these are some hormones and pesticides. Most veterinary drugs are not volatile and cannot be analyzed by GC.

Most studies at the Office of Research use LC, which only requires that the compounds be soluble in liquid. LC has been available as a separation tool since the late 1960s-early 1970s. However, its usefulness was limited by the detectors that were then available.

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CVM Researchers Use Latest Science... *(Cont.)*

Separated compounds in the gaseous or liquid effluent from a chromatograph are detected by a variety of means. The least expensive and most widely available detectors for LC depend on ultraviolet (UV) or visible light (vis) absorbance of the compounds. These detectors are very reliable and easy to use, but not very selective. They are routinely used by most analytical laboratories, but samples analyzed by LC-UV/vis must be fairly clean, meaning the extraction and cleanup is usually long, tedious, and focuses on one or a few compounds. Fluorescence detectors are slightly more expensive, and offer greater selectivity, but the compounds must either have a native fluorescence or be chemically modified to fluoresce.

The most versatile detectors at the Office of Research, and the most expensive, are mass spectrometers. In the late 1980s, practical and effective interfaces became available to couple LC to MS for maximum separation/information about samples.

Mass spectrometry

Mass spectrometry, as used at Office of Research and other state-of-the-art laboratories, is an instrumental method in which the chemical makeup of a substance is identified by its molecular mass. A mass spectrometer is an instrument that measures the masses of individual molecules that have been converted into gaseous ions—in other words, molecules that have been both vaporized and electrically charged. Mass spectrometers use magnetic fields, electric fields, or both to separate a stream of charged particles or gaseous ions according to their mass and charge. The results are recorded onto a computer drive and may be displayed in a graph-like output called a mass spectrum.

Michelle Smith, a CVM Staff Fellow from the Oak Ridge Associated Universities, and CVM chemist David N. Heller examine samples prepared for LC/MS/MS analysis in an Office of Research laboratory at CVM's facilities in Laurel, MD.

The technique of mass spectrometry had its beginnings in the early 20th century. Originally, the spectrometer was confined almost entirely to the world of physics, where the tool was used to discover a number of isotopes and measure their atomic masses. As the cost of mass spectrometry has plummeted, mass spectrometers have become increasingly available in well-equipped laboratories.

Today, a mass spectrometer ranges in size from about the size of an ordinary home oven to large instruments that can fill whole rooms.

The mass sorting and detection processes that occur in a mass spectrometer require samples to be a gas. However, modern developments allow liquid samples to be introduced because liquids can be volatilized at the inlet to the device's vacuum chamber.

Instead of a single substance or family of substances, the mass spectrometer can provide information from a single sample simultaneously on as many as four dozen substances or more, allowing the mass spectrometer, particularly when used in conjunction with a liquid chromatograph, to be used both as for screening and detailed analysis.

Mass spectrometry is a powerful analytical technique that is used to identify unknown compounds, to quantify known compounds, and to reveal the structure and chemical properties of molecules. In simpler terms, a mass spectrometer electronically "weighs" molecules by determining their molecular mass. This means compounds can be identified at extremely low concentrations in chemically complex mixtures.

Liquid chromatography with tandem mass spectrometry

When a mass spectrometer is connected to the end of a chromatographic column in a manner similar to the other detectors, the result is a powerful analytic instrument. Use of liquid chromatography

(Continued, next page)

BSE INSPECTION UPDATE

CVM Reports BSE Inspection Figures as of March 5

As of March 5, 2005, the Food and Drug Administration (FDA) had received more than 35,000 reports of inspections done under the ruminant feed rule designed to prevent the establishment and spread of bovine spongiform encephalopathy (BSE) in the United States.

Approximately 70 percent of the inspections were conducted by State officials under contract to FDA, with the remainder conducted by FDA officials.

Inspections conducted by State and FDA investigators are classified to reflect the compliance status at the time of the inspection, based upon whether objectionable conditions were

(Continued, next page)

CVM Researchers Use Latest Science... *(Cont.)*

with mass spectrometry is increasingly common at Office of Research and other laboratories. The power of this technique is in the production of multiple readouts instead of a simple electronic signal that measure the amount of a specific substance from each of the substances detected. Thus, this technique can rapidly determine both the identity and quantity of a number of unknown components.

Structural information for a substance can be read with a high degree of specificity when specialized tandem mass spectrometers are used. A tandem mass spectrometer can be thought of as two mass spectrometers in series connected by a chamber or collision cell in which a molecule is broken into its component parts. A sample is "sorted" and "weighed" in the first mass spectrometer, then broken up in the collision cell, where its components are sorted and weighed in the second mass spectrometer. So the tandem mass spectrometer is able to fragment or separate the substances in a sample and analyze the products that are generated.

Another way of looking at how tandem mass spectrometers work is the analogy of sorting pocket change. Each coin in a pocketful of change has a unique weight and size—quarters weigh more and are bigger than dimes. A person can sort the coins by weight and size without even looking; then the quantity of each type of coin can be counted quickly. Tandem mass spectrometers can take the sorting even further, like adding vision to the coin sorting process. For example, a person who looks at quarters can, by their specific designs, identify ordinary quarters and each of the new State quarters, and separate them further by their slightly different structures, even though each has a similar

Mary C. Carson (center), Ph.D., a CVM chemist, discusses LC/MS/MS analytical results with Staff Fellow Michelle Smith (left) and CVM chemist David N. Heller in an Office of Research laboratory in Laurel, MD.

weight and size. A tandem mass spectrometer can quickly sort biochemically important molecules of similar weight just as a person can look at the pocket change and sort out how many of the different state coins the person has.

Accordingly, LC/MS/MS techniques can be automated and give high throughput in new analytical and diagnostic methods. Many of the procedures used in human clinical diagnostics also find applications in food and veterinary diagnostics (clinical chemistry, bacteriology, enzyme immunoassays, molecular diagnostics) in meat and fatty tissues, seafood, milk, honey, and processed materials such as feeds.

...BSE Inspection Figures as of March 5 *(Continued)*

documented. Based on the conditions found, inspection results are recorded in one of three classifications:

- **OAI (Official Action Indicated)** when inspectors find significant objectionable conditions or practices and believe that regulatory sanctions are warranted to address the establishment's lack of compliance with the regulation. An example of an OAI classification would be findings of manufacturing procedures insufficient to ensure that ruminant feed is not contaminated with prohibited material. Inspectors will promptly re-inspect facilities classified OAI after regulatory sanctions have been applied to determine whether the corrective actions are adequate to address the objectionable conditions.
- **VAI (Voluntary Action Indicated)** when inspectors find objectionable conditions or practices that do not meet the threshold of regulatory significance, but warrant an advisory to inform the establishment that inspectors found conditions or practices that should be voluntarily corrected. VAI violations are typically technical violations of the 1997 BSE Feed Rule. These violations include minor recordkeeping lapses or conditions involving non-ruminant feeds.
- **NAI (No Action Indicated)** when inspectors find no objectionable conditions or practices or, if they find objectionable conditions, those conditions are of a minor nature and do not justify further actions.

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*(**Note:** The following figures are as of March 5.)*

Renderers

These firms are the first to handle and process (i.e., render) animal proteins. After they process the material, they send it to feed mills and/or protein blenders for use as a feed ingredient.

- **Number of active firms whose initial inspection has been reported to FDA** – 255
- **Number of active firms handling materials prohibited from use in ruminant feed** – 169 (66 percent of those active firms inspected)

  Of those 169 firms:
  - ❖ 1 (0.6 percent) was classified as OAI
  - ❖ 6 (3.5 percent) were classified as VAI

Licensed feed mills

- In the inspection report database, FDA lists medicated feed licensed feed mills separately from non-licensed feed mills. But the licensing has nothing to do with handling prohibited materials under the feed ban regulation. FDA requires feed mills to have medicated feed licenses to manufacture and distribute feed using certain potent drug products, usually those requiring some pre-slaughter withdrawal time, to produce certain medicated feed products.
- **Number of active firms whose initial inspection has been reported to FDA** – 1,066
- **Number of active firms handling materials prohibited from use in ruminant feed** – 402 (38 percent of those active firms inspected)

  Of those 402 firms:
  - ❖ 1 (0.2 percent) was classified as OAI
  - ❖ 9 (2.2 percent) were classified as VAI

Feed Mills Not Licensed by FDA

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

- **Number of active firms whose initial inspection has been reported to FDA** – 5,133
- **Number of active firms handling materials prohibited from use in ruminant feed** – 1,785 (35 percent of those active firms inspected)

  Of those 1,785 firms:
  - ❖ 4 (0.2 percent) were classified as OAI
  - ❖ 30 (1.7 percent) were classified as VAI

Protein blenders

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

- **Number of active firms whose initial inspection has been reported to FDA** – 302
- **Number of active firms handling materials prohibited from use in ruminant feed** – 86 (28 percent of those active firms inspected)

  Of those 86 firms:
  - ❖ 0 were classified as OAI
  - ❖ 3 (3.5 percent) were classified as VAI

Renderers, feed mills, protein blenders

This category includes any firm that is represented by any of the above four categories, but includes only those firms that manufacture, process or blend animal feed or feed ingredients using prohibited materials.

- **Number of active renderers, feed mills, and protein blenders whose initial inspection has been reported to FDA** – 6,526
- **Number of active renderers, feed mills, and protein blenders processing with prohibited materials** – 568 (8.7 percent of those active firms inspected)

  Of those 568 firms:
  - ❖ 6 (1.1 percent) were classified as OAI
  - ❖ 22 (3.9 percent) were classified as VAI

(Continued, next page)

...BSE Inspection Figures as of March 5 *(Continued)*

Other firms inspected

Examples of such firms include ruminant feeders, on-farm mixers, pet food manufacturers, animal feed salvagers, distributors, retailers and animal feed transporters.

- **Number of active firms whose initial inspection has been reported to FDA** – 12,009
- **Number of active firms handling materials prohibited from use in ruminant feed** – 3,001 (30 percent of those active firms inspected)

Of those 3,001 firms:

- ❖ 11 (0.4 percent) were classified as OAI
- ❖ 89 (3.0 percent) were classified as VAI

Total Firms

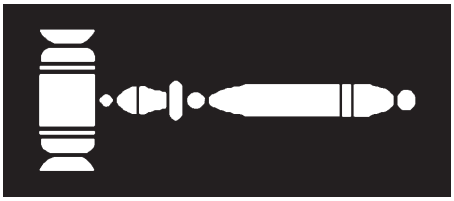
- **Number of active firms whose initial inspection has been reported to FDA** – 15,249
- **Number of active firms handling materials prohibited from use in ruminant feed** – 3,804 (25 percent of those active firms inspected)

Of those 3,804 firms:

- ❖ 13 (0.3 percent) were classified as OAI
- ❖ 95 (2.5 percent) were classified as VAI

*(**Note:** A single firm that has more than one function can be listed in different industry segments, which also means that the total may be less than a combination of all the segments.)*

Regulatory Activities



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

- David L. and Nancy E. Huebner, Owners, Huebner Farm, Columbus, WI
- Daniel W. Thuemmel, President, Thuemmel Dairy, Inc., Port Austin, MI
- Jay L. DeJong, Owner, Rhody Dairy, Sumas, WA

The above violations involved penicillin, gentamicin, and flunixin in dairy cows.

Warning Letters were issued to Roger Nutsch, Partner, U R Farms, Jerome, ID; Daniel W. Nolan, Owner, Nolan Livestock, Bonduel, WI; and Laurens A.T.M. Schilderink, President, Spandet Dairy, Inc., Hart, TX, because investigations found they were offering animals for slaughter that contained illegal tissue residues. The investigations further revealed deviations from rules for Extralabel Drug Use in Animals. The extralabel use of approved animal drugs by veterinarians is allowed by law, provided that the regulations contained in 21 CFR Part 530 are followed. Extralabel use of an approved animal drug that is not in compliance with the regulations renders the drug unsafe under Section 512 and thus adulterated under Section 501(a)(5) of the Federal Food, Drug, and Cosmetic Act (the Act.).

A Warning Letter was issued to Joseph A. Gingerich, Co-Owner, Prime Veal Feed, Ltd., Kensington, OH, for selling and dispensing veterinary prescription drug products without a lawful order from a licensed veterinarian, which caused the products to be misbranded within the meaning of Section 503(f)(1)(C) of the Act. Examples of veterinary prescription drugs dispensed without the order from a licensed veterinarian include Banamine (flunixin meglumine), Micotil (tilmicosin), and Nuflor (florfenicol). In addition, these prescription veterinary drugs were misbranded within the meaning of 502(f)(1) of the Act 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." Inspection also revealed the firm dispensed Flunixin Meglumine Injection bearing a Dexamethasone label and Selenium-Vitamin E Injection (Mu-Se) bearing an Amoxicillin label. These drugs are misbranded under section 502(a) of the Act, because labeling is false or misleading, and 502(i)(3), in that they were offered for sale under the name of another drug. In addition, the inspection found the dispensing of human prescription drugs, such as Sulfamethoxazole and Trimethoprim tablets, Cephalexin capsules, and Amoxicillin capsules, for extralabel use in animals.

A Warning Letter was issued to Alan O. Bostick, President, Sunshine Mills, Inc., Red Bay, AL, because inspection at his feed manufacturing facility in Tupelo, MS, revealed significant deviations from the requirements sent forth in Title 21, Code of Federal Regulations (CFR), Part 589.2000 – Animal Proteins Prohibited in Ruminant Feed. This regulation is intended to prevent the establishment and amplification of bovine spongiform encephalopathy. The inspection indicated the manufacturing of products containing beef meat and bone meal that require the cautionary statement, "Do not feed to cattle or other ruminants," and the firm failed

(Continued, next page)

Regulatory Activities *(Continued)*

to label the products with this statement. Specifically, the products that contained protein derived from mammalian tissues, but lacked the required statement included "Happy Fishman" and "Premier" catfish feeds.

A Warning Letter was issued to William B. Parrish, Chairman of the Board, Parrish & Heimbecker, Limited, Winnipeg, Manitoba, Canada, because inspection of his feed mill operation, Conway Feed, Inc., located in Conway, WA, found significant deviations from the requirements set forth in 21 CFR 589.2000. The investigation found that because the operation failed to adequately inspect the label of a raw material, an ingredient with the cautionary statement "Do not feed to cattle or other ruminants" was used in the manufacture of the finished product Game Bird Crum/Pellet. This final product did not display the cautionary statement that is required because this fish meal may contain prohibited animal proteins. Any product produced from the fish meal must also have the cautionary label. The investigation also revealed that the label of the Game Bird Crum/Pellet feed did not list fish meal as an ingredient. According to the information collected during the inspection fish meal is routinely added to this ration. Pursuant to 21 CFR 501.4(a), all ingredients required to be listed on the label in descending order of predominance by weight.

Correction

The November/December 2004 issue of FDA Veterinarian incorrectly listed in the Regulatory Activities section the location of Lake Country Veterinary Service, P.S. It is in Albany, MN.

CVM Personnel Comings and Goings

New Hires

OFFICE OF MANAGEMENT

- Susan Banks, Management Analyst
- Kathie Foley, Management Officer
- Jackie Salter, Program Analyst
- Sandy Shutts, Program Support Assistant
- Arleen Wang, Program Analyst
- Elaine Johanson, Supervisory IT Specialist

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Robert Abugov, Math Statistician
- Yoko Adachi, Staff Fellow (Math Statistician)
- Mary Allen, Biologist
- Renee Blosser, Microbiologist
- Edward Chen, Staff Fellow (VMO)
- Siobhan DeLancey, Consumer Safety Officer
- Sujaya Dessai, Consumer Safety Officer
- Jude Fiorini, Staff Fellow (VMO)
- Joshua Hayes, Staff Fellow (Microbiologist)
- Laura Huffman, Consumer Safety Officer
- Jeffrey Jones, Staff Fellow (VMO)
- Toni McCannon, Management Officer
- Robin Nguyen, Consumer Safety Officer
- Amy Omer, Staff Fellow (VMO)
- Rebecca Owen, Staff Fellow (Chemist)
- Virginia Recta, Staff Fellow (Math Statistician)
- Eric Silberhorn, Biologist
- Ann Stohlman, Staff Fellow (VMO)
- Michelle Timmerman, Staff Fellow (Microbiologist)
- Jayne Tung, Staff Fellow (VMO)
- Adele Turzillo, Staff Fellow (VMO)
- Denzil Walker, Writer-Editor
- Bonnie Bodo, Biologist
- Nadine Steinberg, Regulatory Counsel

OFFICE OF RESEARCH

- Jamie Cranford, Biologist
- Jewell Washington, Biologist
- Jason Abbott, Microbiologist

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Paul Bachman, Consumer Safety Officer
- Randal Arbaugh, Consumer Safety Officer
- Margaret Bowman Sirolli, Staff Fellow (VMO)

Departures

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Laura Adams, Chemist
- Naba Das, Veterinary Medical Officer
- Wendolyn Jones, Pharmacologist
- Patreese Morton, Applications Examiner
- Tammy Massie, Math Statistician
- Lakisha Preston, Secretary
- Kyunghee Song, Math Statistician
- Juandy Walston, Management Officer

OFFICE OF RESEARCH

- Stanley Serfling, Biologist
- Mark Hirshenson, Biological Aide

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Confidence Gbarayo, Regulatory Review Officer
- Francisca Stone, Industry Compliance Specialist

Approvals for November and December 2004

CVM has published in the *Federal Register* notice the approval of these New Animal Drug Approvals (NADAs)

- REBALANCE Antiprotozoal Oral Suspension (sulfadiazine/pyrimethamine) filed by Animal Health Pharmaceuticals, LLC. (NADA 141-240). The NADA provides for veterinary prescription use of an oral suspension of sulfadiazine and pyrimethamine for the treatment of equine protozoal myeloencephalitis (EPM) caused by Sarcocystis neurona. Notice of approval was published December 2, 2004.

CVM has published in the *Federal Register* notice the approval of these Supplemental New Animal Drug Approvals (NADAs)

- PULMOTIL 90 (tilmicosin phosphate) Type A medicated article filed by Elanco Animal Health (NADA 141-064). The supplemental NADA provides for the use of the product in swine feed for the control of swine respiratory disease associated with certain bacterial organisms. The supplemental NADA provides for revised reproductive safety labeling. Notice of approval was published December 30, 2004.

- FINAPLIX-H (trenbolone acetate) filed by Intervet, Inc. (NADA 138-612). The supplemental NADA provides for the addition of statements to labeling warning against the use of the product in calves to be processed for veal. Notice of approval was published December 2, 2004.

- SYNOVEX C and SYNOVEX S (progesterone and estradiol benzoate) filed by Fort Dodge Animal Health, Division of Wyeth (NADA 009-576). The supplemental NADA provides for the addition of statements to labeling warning against the use of these products in calves to be processed for veal. Notice of approval was published in December 2, 2004.

- COMPONENT E-C and COMPONENT E-S (progesterone and estradiol benzoate), and COMPONENT E-C with TYLAN and COMPONENT E-S with TYLAN (progesterone and estradiol benzoate with tylosin tartrate) filed by Ivy Laboratories, Division of Ivy Animal Health, Inc. (NADA 110-315). The supplemental NADA provides for the addition of statements to the labeling warning against the use of these products in calves to be processed for veal. Notice of approval was published December 2, 2004.

- METACAM (meloxicam) Solution for Injection filed by Boehringer Ingelheim Vetmedica, Inc. (NADA 141-219). The supplement provides for use of the product in cats for control of postoperative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration when administered prior to surgery, and also revises dosage information for use of this product in dogs. Notice of approval was published November 30, 2004.

- METACAM (meloxicam) Oral Suspension filed by Boehringer Ingelheim Vetmedica, Inc. (NADA 141-213). The supplemental NADA provides revised dosage information for use of the product dogs. Notice of approval was published November 30, 2004.

- RUMENSIN 80 (monensin sodium) Type A medicated article to formulate Type B and Type C medicated feeds filed by Elanco Animal Health, Division of Eli Lilly & Co. (NADA 095-735). The supplemental NADA provides for use of monensin Type A medicated

(Continued, next page)

Approvals for November and December 2004 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

articles to formulate Type B and Type C medicated feeds used for increased milk production efficiency (production of marketable solids-corrected milk per unit of feed intake) in dairy cows. Notice of approval was published November 26, 2004.

- REVALOR (trenbolone acetate and estradiol) implants filed by Intervet, Inc. (NADAs 140-897 and 140-992). The supplemental NADAs provide for the addition of statements to labeling of subcutaneous implants containing trenbolone acetate and estradiol warning against the use of the products in calves to be processed for veal. Notice of approval was published November 24, 2004.

- SYNOVEX H (estradiol benzoate and testosterone propionate) filed by Fort Dodge Animal Health, Division of Wyeth (NADA 011-427). The supplemental NADA provides for the addition of statements to labeling of subcutaneous implants containing estradiol benzoate and testosterone propionate warning against the use of these products in calves to be processed for veal. Notice of approval was published November 24, 2004.

- COMPONENT E-H (estradiol benzoate and testosterone propionate) and COMPONENT E-H with TYLAN (estradiol benzoate and testosterone propionate with tylosin tartrate) filed by Ivy Laboratories, Division of Ivy Animal Health (NADA 135-906). The supplemental NADAs provide for the addition of statements to labeling of subcutaneous implants containing estradiol benzoate and testosterone propionate warning against the use of these products in calves to be processed for veal. Notice of approval was published November 24, 2004.

- ENCORE (estradiol) and COMPUDOSE (estradiol) filed by Ivy Laboratories, Division of Ivy Animal Health, Inc. (NADA 118-123). The supplemental NADA provides for the addition of statements to labeling of subcutaneous implants containing estradiol warning against the use of these products in calves to be processed for veal. Notice of approval was published November 22, 2004.

- SYNOVEX PLUS (trenbolone acetate and estradiol benzoate) and SYNOVEX CHOICE (trenbolone acetate and estradiol benzoate) filed by Fort Dodge Animal Health, Division of Wyeth (NADA 141-043). These two subcutaneous implants products are used in steers and heifers fed in confinement for slaughter for increased rate of weight gain and/or improved feed efficiency. The supplemental NADA provides for the addition of statements to labeling of subcutaneous implants containing trenbolone acetate and estradiol benzoate warning against the use of these products in calves to be processed for veal. Notice of approval was published November 22, 2004.

CVM has published in the *Federal Register* notice the approval of these Abbreviated New Animal Drug Approvals (ANADAs)

- Furosemide Syrup 1% (furosemide) filed by Phoenix Scientific, Inc. (ANADA 200-382). The ANADA provides for veterinary prescription use of furosemide syrup in dogs by oral administration for treatment of edema associated with cardiac insufficiency and acute noninflammatory tissue edema. Phoenix Scientific's Furosemide Syrup 1% is approved as a generic copy of Intervet, Inc.'s LASIX (furosemide) Syrup 1%, approved under NADA 102-380. Notice of approval was published December 14, 2004.

(Continued, next page)

Approvals for November and December 2004 *(Continued)*

CVM has published in the *Federal Register* notice the approval of these Supplemental Abbreviated New Animal Drug Approvals (ANADAs)

- COMPONENT T-H and COMPONENT T-S (trenbolone acetate), COMPONENT T-H with TYLAN and COMPONENT T-S with TYLAN (trenbolone acetate with tylosin tartrate) filed by Ivy Laboratories (ANADA 200-224). The supplemental ANADA provides for the addition of statements to the labeling warning against the use of these products in calves to be processed for veal. Notice of approval was published December 2, 2004.

- COMPONENT (trenbolone acetate and estradiol) implants and COMPONENT plus TYLAN (trenbolone acetate and estradiol with tylosin tartrate) implants filed by Ivy Laboratories, Division of Ivy Animal Health (ANADAs 200-221 and 200-346). The supplemental ANADAs provide for the addition of statements to labeling of subcutaneous implants containing trenbolone acetate and estradiol warning against the use of the products in calves to be processed for veal. Notice of approval was published November 24, 2004.

- SYNOVEX (trenbolone acetate and estradiol) implants filed by Fort Dodge Animal Health, Division of Wyeth (ANADA 200-367). The supplemental ANADA provides for the addition of statements to labeling of subcutaneous implants containing trenbolone acetate and estradiol warning against the use of the products in calves to be processed for veal. Notice of approval was published November 24, 2004.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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