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FDA Issues Recordkeeping Regulation Under Bioterorrism Act, Completing the Requirements of Law

By Jon F. Scheid, Editor

In early December, the Food and Drug Administration (FDA) issued the final regulation about the recordkeeping requirements under the Bioterrorism Act of 2002, the fourth set of regulations the act requires.

The recordkeeping rule requires persons who handle food, including feed and pet food, to maintain records that indicate the source of the food or ingredients and the destination for the products. These are the records that FDA inspectors will need to have to investigate credible threats of bioterrorism.

The other three rules apply to registration of firms, prior notice of food shipments imported or offered for import into the United States, and detention of products that FDA authorities believe pose a threat of injury.

Records rule

According to the recordkeeping rule, which was published December 6, 2004, "persons who manufacture, process, pack, transport, distribute, receive, hold, or import food" are required to establish and maintain records that identify the immediate previous source of all foods received, and that identify the subsequent recipient of the food product.

How long the records must be maintained depends on the type of food product. Records about animal feed and pet food must be maintained for a year, which corresponds to the time feed manufacturers are required to keep records under the BSE feed rule.

Companies employing 500 persons or more must comply with the rule within a year of its publication. Mid-sized firms with between 11 and 499 employees must comply within 18 months. And small firms employing 10 or fewer persons must comply within 24 months.

When FDA has a reasonable belief that an article of food is adulterated and presents a threat of serious adverse health consequences or death to humans or animals, the final rule requires that firms make records available to FDA inspectors as soon as possible, but in no case more than 24 hours after receiving the request. Draft guidance for FDA staff exercising records access authority has been published and can be accessed at *http://www.cfsan.fda.gov/~dms/secgui12.html*.

The regulation requires firms to create records when they receive food or feed, release it, or transport it. For non-transporters the records must identify the immediate non-transporter previous *sources*, whether foreign or domestic, of all foods received, as well as the immediate subsequent non-transporter *recipients* of all foods released. The information must include:

- The name of the firm;
- Its address, phone number, and e-mail address, if available;
- Type of feed or food including brand name and specific variety; date released;
- Quantity and type of packaging; and
- Identity of the immediate subsequent transporter recipients, including the name, address, telephone number, and if available, fax number and e-mail address.

Firms that manufacture, process, or pack food must also include lot or code numbers or other identifiers, if such information exists.

For transporters, records have to include names of the transporter's immediate previous source and the transporter's immediate subsequent recipient, origin and destination points, the date shipment was received and the date it was released, number of packages, description of freight, route of movement during the time the food was transported,

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and transfer point(s) through which the shipment moved.

Persons who transport food in the U.S. have five alternative methods of meeting the requirements of the rule. These are explained at *http://www.cfsan.fda.gov/~dms/fsbtac23.html*.

Concerning the source of the food or feed ingredients, the recordkeeper must be as specific as possible about the source. For instance, if a feed mill received grain from three separate elevators and segregates the grain into different storage bins, the feed mill should be able to report the source of the grain in each bin. However, if the grain is commingled, the records should indicate all three sources for the grain.

FDA is flexible about what records it will accept. The records can be kept in any paper or electronic format the recordkeeper wants, as long as they provide the required information. Firms do not have to create duplicate records. So records kept for the BSE rule, for instance, could be used for the Bioterrorism rule, if they supply the required information.

The rule says that the records must either be kept at the establishment where the food or feed products are handled, or made available at a reasonably accessible location.

Records relating to recipes, financial data, pricing data, personnel data, research and sales data are excluded from the recordkeeping requirements. A recipe is defined as a formula, including ingredients, quantities, and instructions for manufacturing a food product. So even though recipes are excluded, records relating to only ingredients of a product, but not the quantities or instructions, are required under the recordkeeping rule.

The rule has some exclusions. For instance, it does not apply to farms. Farmers selling grain directly to a feed manufacturer do not have to keep records of that sale. However, the feed manufacturer will have to have a record showing the farmer who supplied the grain. When a feed mill buys grain from a commercial supplier, though, such as a commercial elevator, both the feed manufacturer and the elevator must have records of the transaction.

Ingredient suppliers, such as protein blenders, mineral supplement suppliers, etc., must keep records of suppliers and customers who are not retail customers.

Firms do not have to keep records of sales direct to consumers. For example, a small, local feed mill that receives ingredients from local farmers and makes its own brand of feed to sell to local farmers should have records of who transported the grain to the feed mill, and which farms supplied the grain. But it does not need to keep records about the retail sales.

Other provisions of bioterrorism rule

Registration, prior notice and administrative detention rules have already gone into effect as either final or interim final rules.

- **REGISTRATION:** The food facilities registration requirement went into effect in October 2003 and initially required all firms that manufacture or process, pack or hold food for human or animal consumption (the rule applies to animal feed and pet food) be registered by December 12, 2003. However, FDA first focused on education. Firms that had not registered by the due date were allowed a grace period to come into compliance before FDA would take action against them.

  (As of December 22, 2004, slightly fewer than 240,000 food firms had registered. FDA is estimating that slightly more than 400,000 firms are required to register.)

  FDA set up a system that allowed firms to register on line at *www.fda.gov/furls*. It also permits paper registrations to be mailed to: U.S. Food and Drug Administration, HFS-681, 5600 Fishers Lane, Rockville, MD 20857, USA, or faxed to 301-210-0247.

  Firms are required to provide the name, address, and phone number for the facility and, if applicable, its parent company. Also, the registrant should provide the name, address, and phone of the owner, operator, or agent in charge; all trade names the facility uses; a statement certifying that the information submitted is accurate and the person submitting the information is the appropriate person to do so; and the applicable food product categories as identified in FDA's regulation (21 CFR 170.3).

  Animal feeds, though, are not identified under that regulation. FDA encourages feed manufacturers to provide information about their products in the optional information section of the registration form.

- **PRIOR NOTICE:** Also in October 2003, FDA announced its regulation requiring food (including animal feed and pet food) importers notify FDA

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FDA VETERINARIAN

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Ask CVM

***Q:** I understand that FDA is reviewing the safety of "Cox 2 inhibitors" human drugs used for pain relief. Will FDA also be reviewing Cox 2 inhibitors approved for use in animals?*

A: No. At this time, FDA does not plan to review the safety of veterinary Cox 2 inhibitor products.

The Center for Veterinary Medicine considers the approved veterinary nonsteroidal anti-inflammatory drugs (NSAIDS), including drugs classified as Cox 2 inhibitors, to be safe and effective when used according to the label and when dog owners are informed about common NSAID side effects.

CVM is constantly screening new Adverse Drug Event (ADE) reports, including those for cardiac ADEs, to determine if the reports contain any unexpected side effects. We have not seen any unexpected side effects for NSAID products.

The concern in human medicine is that the use of Cox 2 inhibitors can lead to heart ailments or strokes. We do not receive many ADEs involving those signs for veterinary NSAIDs or other drugs. Part of the reason for that is the considerable difference between the diagnostic procedures for pets and for humans and the difference in reporting of ADEs. While it is extremely common for physicians to diagnose heart attacks and strokes in humans, it is extremely uncommon for veterinarians to diagnose them in dogs. Most veterinarians do not order MRIs or CT scans for animals, even though those are common diagnostic tools for humans.

The concern in human medicine is that the use of Cox 2 inhibitors can lead to heart ailments or strokes

Another reason is that dogs rarely suffer lethal heart attacks. Dogs grow good collateral circulation in the heart, but humans do not.

CVM will continue to monitor these and other veterinary drugs and look for unusual frequency and severity of side effects. If, as in the case of the human drugs, we find new and conflicting scientific data on adverse events associated with an approved drug, we will take appropriate action. ■

FDA Issues Recordkeeping Regulation Under Bioterorrism Act... *(Continued)*

in advance of the shipment's arrival. This rule went into effect December 12, 2003.

Prior Notice must be submitted electronically, either through the Automated Broker Interface/Automated Commercial System (ABI/ACS) of the Bureau of Customs and Border Protection (CBP), or through FDA's Prior Notice System Interface at *http://www.accessfda.gov*. Importers must provide much the same information they were already submitting to CBP prior to the Prior Notice rule. That information includes:

– Identification of the person submitting the information or the person transmitting the information;

– Entry type and CBP identifier;

– Identification of the type of food and an estimate of the quantity to be imported;

– Identification of the manufacturer or, if known, grower;

– The FDA country of production;

– The shipper, unless the product is coming in by mail;

– The identification of the importer, owners and ultimate consignee (except for food being transshipped through the United States);

– Identification of the carrier; and

– Planned shipment information.

FDA must be notified of a shipment no more than 5 days in advance, and no less than 2 hours if the shipment is coming by road, 4 hours if coming by air or rail, and 8 hours if coming by water.

- **ADMINISTRATIVE DETENTION:** The Bioterrorism Act also gives FDA the authority to take control of an imported food or feed product if FDA "has credible evidence or information indicating such article presents a threat of serious adverse health consequences or death to humans or animals," according to a fact sheet FDA issued in May, 2004.

FDA points out that its authority for administrative detention is different from its right to refuse entry of product. FDA can exercise its authority to refuse entry of an imported product into the United States when it determines that the product was not properly or safely produced, packed, or held. FDA will use its right for administrative detention when it believes the product could be part of a terrorism attempt.

The administrative detention provisions of the act took effect immediately upon enactment of the Bioterrorism Act. ■

CVM Selects Sharon Benz to Head Animal Feeds Division

The Center for Veterinary Medicine (CVM) announced in November that Dr. Sharon Benz has accepted the position of Director of CVM's Division of Animal Feeds.

Dr. Benz replaces Dr. George Graber, who was selected earlier in 2004 for the post of Deputy Director of the Office of Surveillance and Compliance.

Dr. Benz holds a Ph.D. in animal science from Virginia Polytechnic Institute and State University. She has been at CVM for 14 years, and has been the leader of the Nutrition and Labeling Team in the Division for the past seven years.

The Division of Animal Feeds reviews animal food additive applications, is responsible for licensing feed mills, and supplies technical support for the bovine spongiform encephalopathy (BSE) rules. It is part of the Office of Surveillance and Compliance. The Division is made up of the feed safety team, the medicated feeds team, and the nutrition and labeling team, which Dr. Benz headed before the promotion.

One of the challenges of the job will be keeping up with the newly evolving sciences, such as genetic engineering of plants and microorganisms, which are the most likely sources of new types of feed ingredients and additives, Dr. Benz said. Increasingly, she said, the Division of Animal Feeds has received food (feed) additive petitions for products made with these new technologies. And she expects the level of science behind such petitions to grow increasingly sophisticated in the future.

Part of Dr. Benz's strategy to meet these demands includes continued hiring of talented and well trained scientists. "We hope to keep hiring good scientists, so that we can keep the science level in the division up-to-date, and continue to stay current in evolving technologies," she said.

Dr. Benz also hopes to begin developing guidance documents that will help provide to the industry information about labeling requirements and information about how to prepare food additive applications. She pointed out that the Food and Drug Administration's Center for Food Safety and Applied Nutrition has prepared many guidances for the food industry it regulates, and the result has been a more transparent review process. CVM currently reviews products on a case-by-case basis, she said. "A guidance explaining what's needed to approve, for instance, feed ingredients derived from genetically modified microorganisms would streamline that process," she added.

Dr. Benz said she was well prepared for her new position, and described her

Dr. Sharon Benz

predecessor, Dr. Graber, as a "good mentor" who helped her learn what was important on the job. Also, in her previous position she gained a great deal of experience through working with the Association of American Feed Control Officials on pet food rules and feed ingredient definitions.

In her new position, Dr. Benz expects to expand her involvement in the Center's Animal Feed Safety System (AFSS) initiative. The goal of AFSS is to develop a national, uniform, risk-based system of rules concerning food safety. CVM held its first public AFSS workshop in 2003, and plans to have another in 2005. The process should be wrapped up in 2007.

CVM Advisory Committee Discusses Withdrawal of Heartworm Product

The Center for Veterinary Medicine's (CVM) advisory committee was scheduled to meet in a public session January 31, 2005, to discuss the voluntary recall of the dog heartworm drug product, ProHeart 6®.

CVM's Veterinary Medicine Advisory Committee (VMAC) is made up of independent experts who provide advice and recommendations to the Food and Drug Administration about regulatory issues.

ProHeart 6's manufacturer, Fort Dodge Animal Health, voluntarily recalled the product in September 2004. CVM has received more than 5,000 Adverse Drug Event reports about the product since it was approved in June 2001. The reports discussed significant and unanticipated problems associated with the use of the drug.

CVM Samples Feed Ingredients for Bacteria Under NARMS

Feed ingredients could be a source of bacteria in the food-animal production environment. Some of those bacteria could be resistant to antimicrobials, creating a public health concern. CVM officials are using the established NARMS program to find out more about this possible link.

by Marcia L. Headrick, DVM, MPH, DACVPM
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Center for Veterinary Medicine NARMS Coordinator
Collaborating Authors: Drs. Joseph Paige, David Wagner, and Robert Walker, FDA CVM

The potential for the selection of antimicrobial resistant bacteria in animal production settings and for those bacteria to negatively affect antimicrobial chemotherapy in human medicine is an important food safety and public health issue. While there may be multiple sources of antimicrobial resistant bacteria in the animal production environment, there are minimal data on the role of animal feeds and the ingredients used to manufacture these feeds in the development and dissemination of antimicrobial resistant bacteria in the animal production environment.

To address this issue, the Center for Veterinary Medicine (CVM) conducted pilot studies as a part of the National Antimicrobial Resistance Monitoring System-Enteric Bacteria (NARMS). The goal of these studies was to collect data on the prevalence of foodborne enteric bacteria present in animal feed ingredients and to determine the antimicrobial susceptibility profile of those isolates.

In addition, this study provided the opportunity to develop laboratory methods for the testing of animal feed ingredients and to determine the feasibility of conducting a nationwide surveillance of animal feeds as part of NARMS.

CVM has divided the program into three phases.

Phase I: animal-derived proteins

The objectives of phase I of the NARMS Animal Feed Ingredient Studies were to:

- Estimate the prevalence of *Salmonella*, *E. coli*, *Campylobacter*, and *Enterococcus* in animal-derived protein feed ingredients;
- Identify *Salmonella* serotype diversity occurring in these commodities; and
- Determine antimicrobial susceptibility profiles of the *Salmonella*, *E. coli*, *Campylobacter*, and *Enterococcus* organisms isolated from the animal feed ingredient samples.

Samples of animal-derived protein ingredients used in animal feeds were collected in 2002 from rendering plants across the United States by the Food and Drug Administration's Office of Regulatory Affairs (ORA) Field Inspectors. Samples were shipped to the CVM's Office of Research for analysis.

Samples of animal-derived protein ingredients used in animal feeds were collected in 2002 from rendering plants across the United States by the Food and Drug Administration's Office of Regulatory Affairs (ORA) Field Inspectors.

Composites were made from these samples and cultured for *Salmonella, E. coli,* and *Campylobacter* as described in the FDA Bacteriological Analytical Manual (BAM). The samples were cultured for *Enterococcus* using methods developed at CVM's Office of Research. All samples were cultured in duplicate. The antimicrobial susceptibility profiles of isolates were determined using NARMS laboratory methods. The antimicrobial agents tested were the same as those used in the NARMS custom panel. National Committee for Clinical Laboratory Standards (NCCLS) interpretive criteria (susceptible and resistant breakpoints) were used when available.

The animal-derived protein feed ingredients cultured for *Salmonella*, *E. coli*, *Campylobacter*, and *Enterococcus* included:

- meat and bone meal (72 samples);
- blood meal (16 samples);
- bone meal (2 samples);
- feather meal (10 samples);
- poultry meal, (17 samples); and
- fish meal (5 samples).

Campylobacter was not isolated from any of the samples whereas *E. coli* was isolated from 40 percent. None of the *E. coli* was enterohemorrhagic *E. coli*.

Forty-two (34 percent) of animal protein derived feed samples were positive for *Salmonella*. There were 70 *Salmonella* isolates recovered and they were distributed into 27 identifiable serotypes. *S.* Tennessee was the most common serotype recovered, but it comprised less than 10 percent of the isolates (6 total).

In general, the *Salmonella* and *E. coli* isolates that the researchers recovered from these feed ingredient commodities were susceptible to all drugs tested, except tetracycline, to which 17 of the *E. coli* isolates were resistant.

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CVM Samples Feed Ingredients . . . *(Continued)*

Enterococcus were isolated from 84 percent of the samples. These isolates were resistant to erythromycin (4.5 percent), penicillin (2 percent), tetracycline (18.5 percent), ciprofloxacin (8 percent), and streptomycin (2.5 percent). There was no resistance detected to quinupristin/dalfopristin (Synercid™) in any of the non-*faecalis Enterococcus* species. All isolates tested were susceptible to vancomycin and linezolid, with the exception of an isolate of *E. gallinarum*, which exhibited intermediate susceptibility to vancomycin.

These data were presented by FDA CVM scientists at the 2003 and 2004 American Society for Microbiology meetings.

Phase II: plant-derived protein

In 2003, 79 samples of plant-derived protein animal feed ingredients were collected as Phase II of the NARMS Animal Feed Ingredient Studies. These animal feed ingredients are primarily by-products of the oilseed industry. However, some cereal based products were received.

The following plant-derived protein animal feed ingredient samples were cultured for *Salmonella*, *E. coli*, and *Enterococcus:*

- alfalfa meal/pellets (14 samples)
- canola meal (2 samples)
- corn (14 samples)
- gluten (2)
- cottonseed meal (8 samples)
- hominy (1 sample)
- linseed meal (3 samples)
- soybean meal (30 samples), and
- sunflower meal (5 samples)

The samples were collected by FDA ORA Field Inspectors from different sources across the United States. Inspectors from the FDA District Offices in Cincinnati, Dallas, Denver, Florida, Kansas City, Los Angeles, Minnesota, New Orleans, and Seattle were involved in collecting and submitting the samples.

Primary isolation and identification of the bacteria have been completed. Susceptibility testing of Phase II plant-derived protein isolates indicated that all *Salmonella* isolates (4 of 79 samples, or 5 percent) tested were susceptible to all 16 antimicrobials tested in the NARMS custom Sensititre panels. Forty-three percent of the plant based feed commodities were positive for *E. coli*. With the exception of tetracyline (9 percent) and cephalothin (13 percent), the 54 *E. coli* isolated were also susceptible to the 16 antimicrobials tested in the NARMS gram negative panel.

Ninety-one percent (72) of samples were positive for *Enterococcus*. A total of 162 enterococci were isolated and tested for susceptibility to 17 antimicrobials. All isolates were susceptible to chloramphenicol, penicillin, vancomycin, and linezolid. In addition, the non-*fecalis* species were susceptible to the streptogramin, quinpristin/dalfopristin (Synercid). Resistance was detected to erythromycin (9.3 percent), tetracycline (9.9 percent), and ciprofloxacin (6.2 percent). High-level kanamycin and streptomycin resistance was detected in 5.5 percent and 1.2 percent of enterococci isolates, respectively.

Phase III: complete feeds

Samples of complete animal feeds will be collected as Phase III of the NARMS Animal Feed Ingredient Studies in 2005. These samples will include approximately 50 samples from swine complete feeds. In addition, the program will include samples from the FDA Feed Contamination Program. Plans for continued sampling, particularly of animal-derived protein feed ingredients, are being considered.

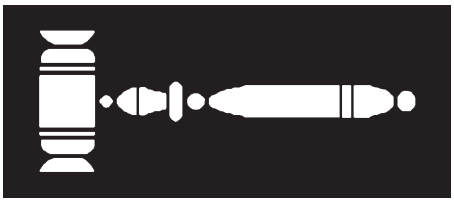
Conclusion

Integrating animal feed data into the ongoing NARMS program will provide data needed to estimate the magnitude of animal feed contamination, understand the sources of contamination, evaluate changes in prevalence and susceptibility patterns of the enteric bacterial isolates over time, and help determine potential mitigation and control strategies to minimize the spread of resistant foodborne pathogens through animal feeds and thus through animal production environments.

Better understanding of the prevalence of antimicrobial resistant bacteria in animal feed ingredients will facilitate development of strategies to interrupt the spread of antimicrobial resistant bacteria to food animals via animal feed ingredients.

Once analysis of the data is complete, summary results of the NARMS Animal Feed Ingredient Studies will be posted on the FDA CVM NARMS web page. For more information on general antimicrobial drug resistance issues, visit CVM's web site at *www.fda.gov/cvm*. NARMS reports are published annually.

Regulatory Activities



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

- Jeremy M. Clayson, Manager, Cedar Arch-North, Firth, ID
- Jeffrey D. Wendler, DVM, Partner; Ron Aardema, Partner; Donald Aardema, Jr., Partner; and Michael Aardema, Partner; St. Bridget Dairy, LOP, Wendell, ID
- Chris J. Parker, Co-Owner, Parker & Sons, LLC, Silver Lake, IN

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Regulatory Activities *(Continued)*

- Dean E. Zimmer, Owner, Zimmer View Dairy, Marietta, OH
- Gene A. Martin, Sauk Centre, MN
- Bernard Choutchourrou, Owner, Choutchourrou Dairy, Caldwell, ID
- Bernardus P. Goedhart, Owner, Vermeer & Goedhart Dairy, Shafter, CA
- Ray Albers, Owner, Heritage Dairy, Ontario, CA

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

A Warning Letter was issued to Mr. Lowell J. Ahl, President, Lowlyn Pharmacies, Inc., doing business as Red Cross Drug, Blanchard, OK, after inspection of the veterinary drug compounding operation disclosed significant violations of the Federal Food, Drug, and Cosmetic Act (the Act). The inspection confirmed the company compounded and distributed veterinary drugs using bulk active pharmaceutical ingredients (APIs). The compounded veterinary drugs were found to be unsafe within the meaning of section 512 of the Act because they are not the subject of approved New Animal Drug Applications, and, as such, are adulterated under section 501(a)(5) of the Act. Sections 512(a)(4) and (5) of the Act, and their implementing regulations, allow some extralabel use of approved animal and human drugs, including compounding from such approved drugs, but these provisions apply only to approved drugs and do not permit compounding from bulk APIs. A significant number of the firm's compounded veterinary drugs appear to be compounded outside the context of a valid veterinarian-client-patient relationship for administration by an end user. Instead, they appear to be sales to veterinarians for use as office stock in their professional practice and/or for further distribution. Another concern is the drugs being compounded could be used in food-producing animals, and therefore could result in unsafe drug residues in edible tissues. Moreover, at least two of the drugs being compounded, nitrofurazone and diethylstilbestrol, are not permitted for extralabel use in food-producing animals because they present a risk to public health.

A Warning Letter was issued to Jerry D. Suther, President, Suther Feeds, Inc., Frankfort, KS, for significant deviations from current Good Manufacturing Practice (cGMP) regulations for medicated feeds. The deviations include equipment that comes in contact with active drug components and feeds in process is not subject to all reasonable and effective procedures to prevent unsafe contamination of manufactured feed; sequential production of medicated feeds is not done on a predetermined basis designed to prevent unsafe contamination of feeds with residual drugs; failure to investigate and implement corrective action when assay results show medicated feeds are not within permissible assay limits; failure to consistently and adequately control the receipt, storage, and inventory of drug products; failure to maintain master records and batch production records as required; failure to maintain distribution records for each shipment of medicated feed; and failure of the firm's mixer/blender study to demonstrate equipments' capability to produce a medicated feed of intended potency.

A Warning Letter was issued to Gary Henry, Co-Owner, West Union, OH, after inspection of the farm found serious violations of the Act. The investigation found that the farm's use of the medicated premixes Bovatec 68 (Lasalocid) and Terramycin 50 (Oxytetracycline) in making the medicated feed for their sheep does not conform to the drug's approved New Animal Drug Applications (NADAs). The combination of the drugs is not approved for use in feed for sheep or at the levels found in a sample of the bulk medicated feed collected at the farm. Thus, the feeds are adulterated under 501(a)(6) of the Act. The medicated feed is further adulterated under section 501(a)(2)(B) because of failure to comply with the current Good Manufacturing Practice (cGMP) regulations for medicated feeds. Examples of the farm's failures to follow cGMPs include not having a measuring device that is adequate to measure the amounts of medicated premix added to their feed, and not having records identifying the formula and date of mixing.

Warning Letters were issued to David L. McMahan, Owner, Redfield Feed Service, Redfield, SD, and to Dayton H. Kloss, Owner, Hitchcock Feed Service, Hitchcock, SD, 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 by the Redfield Feed Service without the order from a licensed veterinarian include sulfamethoxazole/trimethoprim, florfenicol, tilmicosin, enrofloxacin, dinoprost tromethamine, and dexamethasone. Examples of veterinary prescription drugs dispensed by Hitchcock Feed Service without an order from a licensed veterinarian include flunixin and florfenicol.

Warning Letters were issued to John H. Newman, DVM, Dublin, TX, and to Neal L. Womack, DVM, and Curtis A. Leyk, DVM, Co-Owners, Lake Country Veterinary Service, P.S., Albany, WI, because investigations revealed serious deviations from extralabel drug use in animals. The extralabel use of approved animal drugs by veterinarians is allowed under the Act 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 Act.

Antimicrobial Drug Delivery in Food Animals and Potential Disruption of Their Intestinal Microflora

The way an antimicrobial drug is administered to food animals may affect the intestinal microflora of the animals, and a potential consequence of the drug delivery is the selection and development of resistant bacteria among the intestinal flora. Here some of the important aspects are discussed to help the reader understand how the intestinal microflora of food animals may be affected at antimicrobial drug delivery.

by S. Steve Yan, Ph.D. and Jeffrey M. Gilbert, Ph.D.
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Current requirements for approval of antimicrobial new animal drugs for food-producing animals (or food animals) in the United States include a rigorous evaluation to ensure that the uses of these drugs are safe and effective for the target food animals, and that they are safe to the environment and to humans that consume food products derived from these animals. Additionally, the manufacturer must demonstrate that it can produce these approved antimicrobial new animal drug products consistent in quality, strength, purity, and potency. Antimicrobial new animal drugs administered to food animals may result in drug residues in the gastrointestinal (GI) tract of the treated animals, and exposure to these drug residues may result in the disruption of the host's intestinal microflora. This exposure may also disrupt the intestinal microflora among food animals and select for resistant bacteria that are foodborne pathogens for humans, causing human food safety concerns. Disruption of the microflora in food animals may be affected by multiple elements. Some of them are briefly described as follows.

1. **Diversity of microflora among food animals.** The intestinal microflora of food animals are established following harmonized host-microorganism equilibrium and may differ significantly among animal species. Food animals include mammalian and non-mammalian species that inhabit terrestrial and aquatic environments, and they also vary widely in size from large species (cattle) to relatively small species (chicken or fish). Considerable variations in their GI anatomies and physiologic functions determine the wide spectrum of intestinal microflora associated with each animal species. Zoonotic, foodborne human pathogens can arise from the intestinal microflora of food animals, and their nature and proportion vary dependent upon animal species. For example, *Campylobacter jejuni* is primarily associated with poultry, while *E. coli* O157:H7 is mainly linked to cattle. Therefore, microbial food safety considerations may vary among different animal species with respect to their resident pathogens.
2. **Properties of antimicrobial drugs.** Substantial information has been accumulated on how antimicrobial drugs work against bacteria, both at the cellular and molecular levels. The response of susceptible bacteria to antimicrobial action *in vitro* is morphologically visible (Figures 1 & 2). Antimicrobials may behave as bacteriostatic or bactericidal agents, and their activities on bacteria are usually drug-specific. Bactericidal or bacteriostatic killing of a given drug is sometimes influenced by measuring conditions, such as inoculum effect, medium pH, ion concentration, etc. Some antimicrobial activities are persistent (i.e., exert a post-antibiotic effect) and remain active at sub-optimal concentrations (i.e., a sub-Minimum Inhibitory Concentration [MIC] effect). Antimicrobial activity may be measured by susceptibility testing performed under standardized *in vitro* conditions. Additionally, many factors may contribute to the ultimate effect of an antimicrobial drug *in vivo*, such as drug protein binding (free drug or unbound can have activity against bacteria), tissue distribution, host immunity status, etc.
3. **Drug delivery in food animals.** Drug delivery methods vary among food animal species, and depend on the purpose for which an antimicrobial is prescribed or ordered, the site of infectious disease and the target pathogen involved, and the drug's properties and formulation. Common delivery routes include parenteral administration (intramuscular or subcutaneous), oral administration (through feed or water), and other delivery methods (intramammary, intrauterine infusion, etc.). Selection of a drug delivery route for a given disease in a given food animal species is a result of a collective consideration of factors such as effectiveness, efficiency, resources, costs,

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Antimicrobial Drug Delivery . . . *(Continued)*

labor intensity, and available drug formulations. Strategies for delivering antimicrobial drugs to food animals will need to continue to evolve as both disease conditions and animal management practices change. Veterinary pharmaceutical companies will continue to fine tune their antimicrobial product formulations and drug delivery regimens to offer the best protection and treatment schemes with delivery systems responsive to emerging needs.

4. **Context matters.** A key piece of information from an antimicrobial drug profile is how much drug will end up in the animal intestine and its effect on the continued equilibrium. This information depends on pharmacokinetic and pharmacodynamic profiles of individual drugs, affected by formulation, route of administration, bioavailability, drug absorption, and transport through the intestinal epithelium, and whether biliary excretion may occur, etc. The drug concentration available in the intestinal lumen is directly linked to whether a potential exposure of intestinal microflora to the drug will actually occur, and to what extent an exposure-response might be. Therefore, such an exposure-response of intestinal microflora needs to be evaluated in a "drug-bacterium" context.

5. **Upon exposure.** A possible consequence of antimicrobial intervention is a disturbance of the intestinal microflora, and the degree of the disturbance will be determined by the individual drug, drug potency, spectrum of activity, dosage regimen, delivery method, working concentration in the intestinal lumen, target food animal species, and the associated intestinal microflora. An important issue is whether a given drug delivery system, under specified use conditions, will negatively impact intestinal microflora so that a resistant population may emerge and thrive, and/or resistant elements may develop and spread. Information is readily

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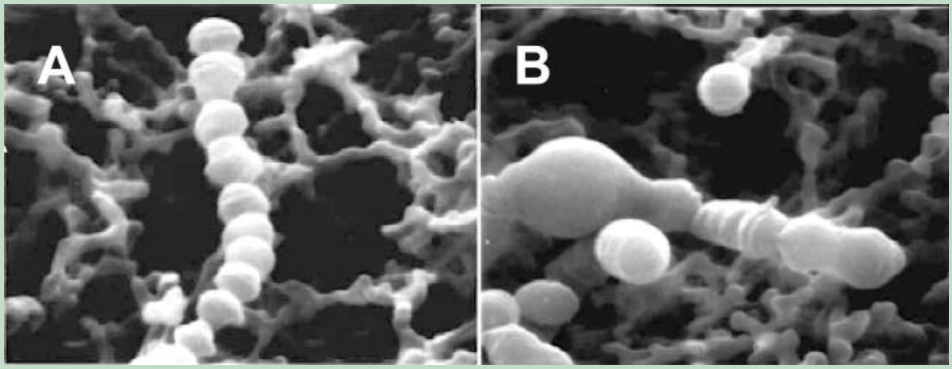

Figure 1. Following in vitro *exposure of streptococci to penicillin at concentration at the MIC or minimum inhibitory concentration, morphological changes (under scanned electro microscopy, at 20,000 X) were obvious in treated cells (B) as compared with controls (A).*

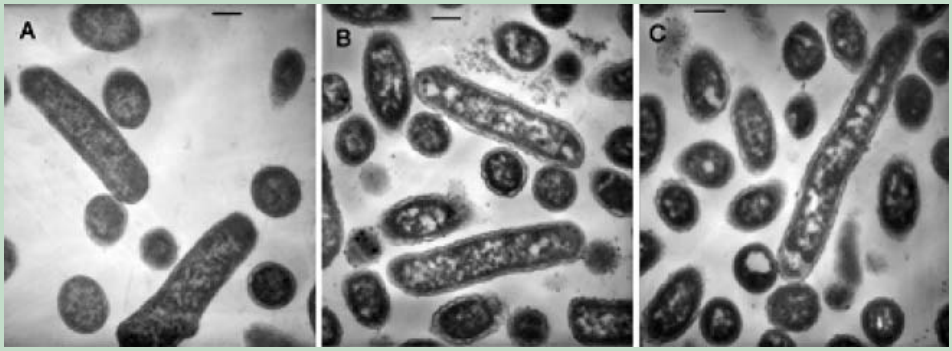

Figure 2. After Escherichia coli in vitro *exposure to a fluoroquinolone drug at a concentration above the MIC (B & C), dramatic morphological changes (under transmission electro microscopy) become visible, including disruption of the cell membrane, disintegration of cytoplasmic contents, and vacuole formation. A = control. The insert bar represents 0.4uM in length.*

Antimicrobial Drug Delivery . . . *(Continued)*

available to indicate that bacteria are able to acquire resistance traits through a variety of mechanisms, including a) inactivation of compounds; b) decrease in membrane permeability or activated efflux function; and c) target modifications. Resistant determinants may be carried on chromosomes or by extra-chromosomal elements, such as plasmids and transposons. Expression of resistant phenotypes may be either inducible or constitutive; thus, evaluation of microbial food safety of antimicrobial new animal drugs can become complicated.

(Note: This article is adopted and modified from a review that appeared in Advanced Drug Delivery Reviews 2004, 56:1497-1521 by the same authors. References used for the current article are not provided due to space limitation but they are included in its original review.)

CVM Seeks Comments on Virginiamycin Prototype Risk Assessment

by Jon F. Scheid, Editor

The Center for Veterinary Medicine (CVM) has completed its virginiamycin risk assessment, which will serve as a prototype for looking at the indirect risks of resistance from the use of antimicrobials in food animals, and is seeking comments on the assessment.

CVM conducted the assessment, which was released in late November, to determine whether pathways exist to link food-animal uses of virginiamycin, a member of the streptogramin class of antimicrobials, with resistance to other streptogramins used in human medicine.

The link is considered to be indirect because virginiamycin is not a drug used in human medicine, but any resistance created through the use of virginiamycin in food-animals potentially could be transferred to *Enterococcus faecium* bacteria that reside in the human gastrointestinal tract. If the human *E. faecium* acquire resistance, treating them with other streptogramins could result in a treatment failure.

The human steptogramin drug of concern is Synercid, which is used in patients who acquire, while being hospitalized, a resistant *E. faecium* infection. According to the risk assessment, as many as 70,000 patients in the United States may acquire a vancomycin-resistant *E. faecium* infection in the hospital each year.

The assumption behind the risk assessment model is that virginiamycin use in food-producing animals could create resistance in *E. faecium* bacteria in the animals. The bacteria could transfer that resistance to other *E. faecium* in the human gastrointestinal system via the consumption of contaminated food products. That resistance would render drugs such as Synercid ineffective.

The risk assessment was designed and developed as a prototype for risk assessments of the indirect transfer of resistance from uses of antimicrobials in food-producing animals. Earlier, CVM conducted a risk assessment of a direct transfer model when it looked at the risk from the use of enrofloxacin in poultry water creating resistant *Campylobacter*, which was transferred via food to humans. (A revised version of the risk assessment was released in January 2001.)

Virginiamycin has been used for food-producing animals for nearly 30 years. However, the Food and Drug Administration's approval of Synercid in 1999 caused concerns about virginiamycin creating a "reservoir" of resistance in animals that might transfer to humans. Synercid and virginiamycin are both steptogramins.

Principles of the risk assessment

In the late 1990s, when CVM first said it would take into account the microbial safety of antimicrobial use for food animals, it adopted a series of principles for determining the risk from the use of any antimicrobial in food animals. The principles are laid out in the Center's Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern."

The first step is hazard identification. A hazard is defined as the possibility that some harm develops from an action, in this case, a threat to public health resulting from the use of an antimicrobial in food-producing animals.

If a hazard is identified, the next step is to assess the extent of the risk. That is done through an assessment of the likely pathways for resistant bacteria to reach people, the extent of exposure people are likely to face to the resistant bacteria, and the consequence of that predicted exposure. Once the risk assessment is complete, officials can determine what risk management steps would be needed.

Conducting the risk assessment

The virginiamycin risk assessment took approximately four years to complete. CVM first announced in 2000 that it would conduct the assessment. At that time, it sought comments about how to

(Continued, next page)

BSE INSPECTION UPDATE

CVM Reports BSE Inspection Figures as of November 6

As of November 6, 2004, the Food and Drug Administration (FDA) had received more than 33,000 reports of inspections done under the ruminant feed rule designed to prevent the establishment and spread of bovine spongiform encephalopathy (BSE) in the United States.

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

Inspections conducted by State and FDA investigators are classified to reflect the compliance status at the time of the inspection, based upon whether objectionable conditions were documented. Based on the conditions found, inspection results are recorded in one of three classifications:

- **OAI (Official Action Indicated)** when inspectors find significant objectionable conditions or practices and believe that regulatory sanctions are warranted to address the establishment's lack of compliance with the regulation. An example of an OAI classification would be findings of manufacturing procedures

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. . . Virginiamycin Prototype Risk Assessment *(Continued)*

go about the assessment, and asked for individuals to submit any data they had.

Dr. Gregg Claycamp and Dr. Barry Hooberman, who conducted the risk assessment, collected data from several sources, including the CVM's National Antimicrobial Resistance Monitoring System, under which CVM is collecting data about bacteria, including resistant bacteria, on retail cuts of meat. Data were also obtained from the Centers for Disease Control and Prevention and from published literature.

Where no data existed, CVM obtained them by commissioning extramural research and buying isolates from hospitals to be tested for resistance. "We went anywhere we could find data," Dr. Hooberman said.

What the risk assessment found

The draft risk assessment reported that streptogramin-resistant *E. faecium* have been found in isolates from poultry and swine sources in both the United States and Europe. It also said that the prevalence of resistance appears to be related to the usage pattern of virginiamycin on the farms.

Further, it said, streptogramin-resistant *E. faecium* was found on food products from animals, and low-level streptogramin resistance occurred at low frequencies in humans outside of hospitals.

The risk assessment concluded that "the transfer of streptogramin resistance determinants from animal *E. faecium* to human *E. faecium* through the foodborne pathway is biologically plausible, but the extent of such transfer *in vivo* cannot be estimated at this time."

According to the risk assessment model, if 10 percent of the Synercid resistance can be attributed to the use of virginiamycin in food-producing animals (with the other 90 percent attributed to the use of Synercid in hospitals), then the food-animal use of virginiamycin may cause from 2 to 37 cases of impaired Synercid human treatment annually due to resistance. If the assumption is that 100 percent of the *E. faecium* resistance to Synercid is a result of the use of virginiamycin in food-animals, then the estimated number of cases of impaired Synercid treatment resulting from the use of virginiamycin in food animals increases by a factor of 10, increasing to 20 to 370 cases annually.

However, the risk assessment also said the resistance genes found on *E. faecium* taken from animal sources appear to be different than those from human isolates.

Comments or additional information

CVM is seeking comments, until February 23, 2005, about the structure of the risk assessment and the data used. Written comments on this draft risk assessment may be sent by February 23, 2005, to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Electronic comments may be sent to: *http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm*. All comments should be identified with Docket Number 2004N-0479. Comments will be considered part of the public record and will be available for viewing on the Internet at *http://www.fda.gov/ohrms/dockets/* and in the FDA Docket room.

The risk assessment was presented in draft form, and as more data become available, CVM can revisit the assessment. Conducting a risk assessment is "an iterative process," Dr. Hooberman said, and whenever additional relevant data become available, the assessment can be revised.

According to the risk assessment, if new data or information become available that can narrow an information gap, the risk estimation can be improved by incorporating the new data into the assessment.

CVM Reports BSE Inspection Figures as of November 6 *(Continued)*

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.

(Note: The following figures are as of November 6.)

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** – 251
- **Number of active firms handling materials prohibited from use in ruminant feed** – 163 (65 percent of those active firms inspected)
- **Of those 163 firms:**
  - ❖ 0 were classified as OAI
  - ❖ 5 (3.1 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** – 1,085
- **Number of active firms handling materials prohibited from use in ruminant feed** – 405 (37 percent of those active firms inspected)
- **Of those 405 firms:**
  - ❖ 2 (0.5 percent) were 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** – 5,107
- **Number of active firms handling materials prohibited from use in ruminant feed** – 1,611 (32 percent of those active firms inspected)
- **Of those 1,611 firms:**
  - ❖ 8 (0.5 percent) were classified as OAI
  - ❖ 25 (1.6 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** – 301
- **Number of active firms handling materials prohibited from use in ruminant feed** – 83 (28 percent of those active firms inspected)
- **Of those 83 firms:**
  - ❖ 1 (1.2 percent) was classified as OAI
  - ❖ 3 (3.6 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** – 6,511
- **Number of active renderers, feed mills, and protein blenders processing with prohibited materials** – 578 (8.9 percent of those active firms inspected)
- **Of those 578 firms:**
  - ❖ 10 (1.7 percent) were classified as OAI
  - ❖ 16 (2.8 percent) were classified as VAI

Other firms inspected

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

- **Number of active firms whose initial inspection has been reported to FDA** – 11,523

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CVM Reports BSE Inspection Figures as of November 6 *(Continued)*

- **Number of active firms handling materials prohibited from use in ruminant feed** – 2,693 (23 percent of those active firms inspected)
- **Of those 2,693 firms:**
  - ❖ 15 (0.6 percent) were classified as OAI
  - ❖ 79 (2.9 percent) were classified as VAI

Total Firms

- **Number of active firms whose initial inspection has been reported to FDA** – 14,853
- **Number of active firms handling materials prohibited from use in ruminant feed** – 3,444 (23 percent of those active firms inspected)
- **Of those 3,444 firms:**
  - ❖ 16 (0.5 percent) were classified as OAI
  - ❖ 89 (2.6 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.)

Sponsors of Growth Hormone Products Change Labels

Sponsors of growth-promoting hormone products for use in cattle have relabeled their products to remind producers that the use of the hormones in veal calves is illegal.

The Center for Veterinary Medicine reported in January that drug sponsors had submitted 16 supplemental applications to update the labels on their approved products to indicate that the products should not be used for veal calves.

The products are implants and contain hormones that are slowly released in the animal's system to enhance growth.

The hormone implants are approved for growth promotion use in cattle, but the approval does not extend to veal calves. Consequently, the use of growth promoting hormone implants for non-ruminating veal calves is illegal. Ruminating cattle are physiologically different than non-ruminating veal calves.

Also, CVM scientists said, because of the differences in the way veal calves and ruminating cattle process and eliminate such hormones, there are no data to show that the animals treated with this product are safe for human consumption or that it is safe and effective for the animal.

In the supplements, the sponsors revised the indications portion of the drugs' labels to state, "Do not use in veal calves. Effectiveness and animal safety in veal calves have not been established." In the warning section, the revised labels state, "A withdrawal period has not been established in pre-ruminating calves. Do not use in calves to be processed for veal."

Food from veal calves that contains the illegal hormone drug is considered adulterated, and veal calf producers who illegally use the hormone products are subject to regulatory action.

Approvals for September and October 2004

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

EQUIMAX Paste (ivermectin 1.87% and praziquantel 14.03% oral paste) filed by Virbac AH, Inc. (NADA 141-215). The supplemental NADA provides for use in breeding, pregnant or lactating mares without adverse effects on fertility. The product is indicated for the use in horses for the treatment and control of various species of the following internal parasites: Tapeworms: *Anoplocephala perfoliata*; Large Strongyles (adults): *Strongylus vulgaris* (also early forms in blood vessels), *S. edentatus* (also tissue stages), *S. equines*, *Triodontophorus* spp.; Small Strongyles including those resistant to some

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Approvals for July and August 2004 *(Continued)*

Supplemental New Animal Drug Applications (Continued)

benzimidazole class compounds (adults and fourth-stage larvae): *Cyathostomum* spp., *Cylicocyclus* spp., *Cylicostephanus* spp., *Cylicodontophorus* spp.; Pinworms (adults and fourth-stage larvae): *Oxyuris equi*; Ascarids (adults and third- and fourth-stage larvae): *Parascaris equorum*; Hairworms (adults); *Trichostrongylus axe*; Large-mouth Stomach Worms (adults); *Habronema muscae*; Bots (oral and gastric stages); *Gasterophilus* spp.; Lungworms (adults and fourth-stage larvae); *Dictyocaulus arnfieldi*; Intestinal Threadworms (adults); *Strongyloides westeri*; Summer sores caused by *Habronema* and *Draschia* spp.; Cutaneous third-stage larvae; and Dermatitis caused by Neck threadworm microfilariae, *Onchocerca* sp. Notice of approval was published September 3, 2004.

BANAMINE (flunixin meglumine) Injectable Solution filed by Schering-Plough Animal Health Corp. (NADA 101-479). The supplemental NADA provides for the veterinary prescription use of flunixin meglumine solution by intravenous injection in lactating dairy cattle for control of pyrexia associated with bovine respiratory disease and endotoxemia, and for control of inflammation in endotoxemia. It also provides for the veterinary prescription use of flunixin meglumine solution by intravenous injection for control of pyrexia associated with acute bovine mastitis and for the establishment of a tolerance for residues of flunixin in milk. Notice of approval was published October 8, 2004.

EQVALAN (ivermectin 1.87 percent) Paste for Horses filed by Merial Ltd. (NADA 134-314). The supplemental NADA provides for revisions to the labeled indications for ivermectin oral paste used in horses. Specifically, under the sub-heading "Small Strongyles," the labeling has been revised to separate the listing of adult species from the fourth-stage larvae. Notice of approval was published October 4, 2004.

EQVALAN (ivermectin) Oral Liquid for Horses filed by Merial Ltd (NADA 140-439). The supplemental NADA provides for revisions to the labeled indications. Specifically, the supplement provides for the use of ivermectin oral liquid for the treatment and control of *Craterostomum acuticaudatum*, *Petrovinema poculatum*, and *Coronocyclus* spp., including *Coronocyclus coronatus* and *Coronocyclus labratus*. The label descriptions of some currently approved parasite genera are also being revised to add included species for which data already exists in the NADA file and to reflect changes in scientific nomenclature. In addition, under the sub-heading "Small Strongyles," the labeling has been revised to separate the listing of adult species from the fourth-stage larvae. Notice of approval was published September 24, 2004.

IVOMEC (ivermectin) Injection for Cattle and Swine filed by Merial Ltd. (NADA 128-409). The supplemental application provides for an increased period of protection from reinfection with three species of internal parasites of cattle following administration of ivermectin solution by subcutaneous injection. Specifically, the period of persistent effectiveness is increased from 14 days to 28 days for *Oesophagostomum radiatum*, and from 14 days to 21 days for *Trichostrongylus axei* and *Cooperia punctata*. A veal calf warning statement is being added because residue depletion data for this class of cattle has not been submitted to the application. Notice of approval was published September 2, 2004.

(Continued, next page)

Approvals for July and August 2004 *(Continued)*

CVM has published in the *Federal Register* notice of the approval of this Abbreviated New Animal Drug Application (ANADA)

NOROMECTIN (ivermectin) Pour On for Cattle filed by Norbrook Laboratories, Ltd. (ANADA 200-272). The application provides for topical use of 0.5 percent ivermectin solution on cattle for the treatment and control of various species of gastrointestinal roundworms (including *Ostertagia ostertagi*), lungworms, grubs, horn flies, sucking and biting lice, and sarcoptic mange mites. Norbrook Laboratories, Ltd.'s NOROMECTIN Pour-On for Cattle is approved as a generic copy of Merial Ltd.'s IVOMEC Pour-On for Cattle, approved under NADA 140-841. Notice of approval was published October 25, 2004.

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

PRAZI-C (praziquantel) Tablets filed by Phoenix Scientific, Inc. (ANADA 200-265). The supplement provides for OTC marketing of the tablets in 5-, 10-, and 50-tablet container sizes for use in the removal of the tapeworms *(Dipylidium caninum* and *Taenia pisiformis)* from dogs and puppies. The OTC pioneer product is marketed in 5-tablet container sizes only. The prescription praziquantel product includes additional labeling claims for use by or on the order of a licensed veterinarian, for removal of the canine cestode *Echinococcus granulosus,* and for removal and control of the canine cestode *Echinococcus multilocularis*. The Phoenix Scientific, Inc.'s PRAZI-C Tablets are approved as a generic copy of Bayer HealthCare LLC's Tape Worm Tabs approved under NADA 111-798. Notice of approval was published October 25, 2004.

Oxytetracycline HCl Soluble Powder-343 filed by Phoenix Scientific, Inc. (ANADA 200-247). The supplement provides for the use of product for skeletal marking of finfish fry and fingerlings by immersion. The approval of this supplemental ANADA relied on publicly available safety and effectiveness data contained in Public Master File (PMF) 5667, which were compiled under National Research Support Project 7 (NRSP-7), a national agricultural research program for obtaining clearances for use of new drugs in minor animal species and for special uses. Notice of approval was published October 22, 2004.

Flunixin Meglumine Injectable Solution filed by Agri Laboratories, Ltd. (ANADA 200-061). The supplement provides for the addition of a claim for veterinary prescription use by intravenous administration for control of fever and inflammation in beef cattle and nonlactating dairy cattle. The Agri Laboratories product is approved as a generic copy of Schering-Plough Animal Health Corp.'s BANAMINE Injectable Solution approved under NADA 111-798. Notice of approval was published September 2, 2004.

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