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FDA's BSE Final Rule Published; New Requirements Imposed on Renderers

by Walt D. Osborne, M.S., J.D., Assistant Editor

After a rulemaking process that took 2-1/2 years, the Food and Drug Administration published on April 25, 2008 (73 F.R. 22720), a final rule that further strengthens existing safeguards against bovine spongiform encephalopathy (BSE) in the United States.

The new rule (21 CFR 589.2001) prohibits the use of the highest risk cattle materials in the food or feed of all animals. This measure augments FDA's 1997 rule (21 CFR 568.2000), which prohibits the use of mammalian-origin proteins in feed fed to ruminants, but allows the use of these materials in feed for non-ruminant animals.

The Agency believes additional protections are needed even though compliance with the 1997 rule has been extremely high, and no new BSE cases have been reported in the United States since March 2006, when the second of two U.S. cases of BSE was detected. The new rule is expected to further reduce any cattle exposure to the BSE agent not eliminated by the 1997 feed rule. It is important to note that new cases of BSE continue to be found in cattle born in the United Kingdom after implementation of that country's ruminant-to-ruminant feed ban. Also, FDA inspections of feed manufacturing firms have identified some instances of inadequate cleanout procedures, mislabeling, and recordkeeping deficiencies.

The new rule, which becomes effective April 27, 2009, is intended to mitigate such compliance failures and prevent the potential transmission of the BSE agent through cross-contamination or on-farm misfeeding.

As discussed in the preamble to the proposed rule, scientific data indicate that roughly 90 percent of BSE infectivity is contained in the brain and spinal cord of cattle, and only about 10 percent of BSE infectivity is present in such cattle parts as the distal ileum of the small intestine, the dorsal root and trigeminal ganglia, and the retina of the eye. For this reason, the new rule focuses on the removal of cattle brain and spinal cord from animal feed.

FDA received more than 800 comments to the October 5, 2005, proposed rule, including comments from industry, State and local governments, trade associations, academia, and consumers. Reviewing all of the comments and responding to them in the preamble to the final rule proved to be a time-consuming task. In particular, comments challenging FDA's estimate of the cost of the new regulation necessitated a re-analysis of the economic impact of the rule. In response to the comments, some changes to the proposed rule are reflected in the final version.

What is prohibited?

FDA's new rule prohibits the use of the following cattle materials in the food or feed of all animals:

- The entire carcass of BSE-positive cattle;
- The brains and spinal cords from cattle 30 months of age and older;
- The entire carcass of cattle not inspected and passed for human consumption that are 30 months of age or older from which brains and spinal cords were not removed;
- Tallow that is derived from BSE-positive cattle; tallow that is derived from other materials prohibited by this rule that contains more than 0.15 percent insoluble impurities; and
- Mechanically separated beef that is derived from the materials prohibited by this rule.

All of these materials constitute "cattle materials prohibited in animal feed," or CMPAF.

One change the Agency made in going from the proposed rule to the final rule concerns the requirement to remove the brain and spinal cord from dead stock cattle, that is, cattle that die of injury or disease before they are ever sent to slaughter. As defined in the proposed rule, CMPAF includes the brains and spinal cords from cattle of any age not inspected and passed for human

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consumption (dead stock cattle), or the entire carcass, if brain and spinal cord were not removed. The rationale for the decision to require brain and spinal cord removal from dead stock cattle of all ages was that European surveillance data shows that cattle not inspected and passed for human consumption were included in the group of cattle at highest risk of BSE. In addition, FDA noted that government inspection personnel were not routinely present in rendering plants to verify the age of dead cattle. FDA specifically requested and received comments on this issue.

As a result, the new rule does not require brain and spinal cord removal from dead stock cattle if the cattle are shown to be less than 30 months of age. FDA made this revision based on comments indicating that it is feasible to put processes in place to age such cattle and that very little risk reduction is gained by excluding material from such cattle. The final rule requires renderers to develop and maintain written procedures for determining the age of and/or removing the brain and spinal cord from dead cattle, and to make the written procedures available for FDA inspection. The recordkeeping requirements for renderers are discussed in greater detail below.

Country exclusion

In response to comments to the proposed rule, FDA revised the final rule so that the Agency may designate a country as not subject to the new requirements. Any country seeking such a designation must submit a written request to the Director of CVM, providing information about that country's BSE case history, risk factors, measures to prevent the introduction and transmission of BSE, and any other information relevant to determining the country's BSE status. Detailed requirements for requesting this designation are set forth in the preamble to the final rule. The Agency may revoke a country's exclusion status if a review of relevant information shows that the country no longer qualifies for the exclusion.

Renderers' responsibilities

During inspections at rendering facilities, FDA intends to verify that renderers maintain records sufficient to demonstrate that material rendered for use in animal feed does not contain CMPAF.

At those rendering establishments that render dead stock cattle for animal feed use, investigators will review written procedures for aging animals and for effectively excluding the brain and spinal cord from animals 30 months of age and older. Investigators will also be verifying that actual practices are effective. The final rule was revised to address comments regarding recordkeeping and the need for verifying that CMPAF has been segregated from raw materials collected from slaughter establishments. The final rule clarifies that a renderer's records must include certification from each supplier, or other documentation acceptable to FDA, that CMPAF has been excluded from materials to be rendered for use in animal feed. Certification or other documentation from the supplier will be considered acceptable, provided it includes a description of the supplier's segregation procedures, a statement by the supplier that its segregation procedures were in place prior to supplying any cattle material to the renderer, and records of the renderer's periodic review of the suppliers' certification or other documentation. Other methods acceptable to FDA, such as third-party certification, may also be used by renderers to document that suppliers have excluded CMPAF from material supplied to the renderer.

...the new rule does not require brain and spinal cord removal from dead stock cattle if the cattle are shown to be less than 30 months of age.

Disposing of CMPAF

As a result of this final rule, a large volume of byproducts from the beef and cattle industries will no longer be allowed to be rendered for animal feed use. Other means of disposing of this material include landfill, composting, incineration, alkaline hydrolysis, and burial. The effective date of April 27, 2009, was established to allow 12 months for new disposal patterns to be developed.

Conclusion

As always, FDA's mission continues to be the protection of public and animal health. This new rule is yet another step FDA is taking to eliminate opportunities for cattle exposure to the BSE agent in feed. It provides a margin of safety by reducing the consequences of inadvertent cross-contamination or on-farm misfeeding, thereby helping to ensure that the U.S. beef supply remains safe.

More information about BSE and the BSE final rule is available on the CVM Web site at *www.fda.gov/cvm/bsetoc.html* .

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CVM Has Significant Role in Regulating Advertising, Labeling of New Animal Drugs

by Carmela Stamper, DVM, Communications Staff, with contributions from Thomas Moskal, DVM, Division of Surveillance, Office of Surveillance and Compliance

The Food and Drug Administration's Center for Veterinary Medicine is responsible for regulating the labeling and advertisements for prescription veterinary drugs and labeling for over-the-counter (OTC) products. Although advertising of OTC products is regulated by the Federal Trade Commission (FTC), CVM still plays a role. When CVM becomes aware of an advertisement for an OTC product that is false or misleading, it can forward this information to the FTC for review and possible action.

Food and drug regulations require sponsors of new animal drugs to submit labeling for prescription and OTC new animal drugs to CVM at the time of initial dissemination of the labeling and require sponsors to provide advertisements for prescription new animal drugs to CVM at the time of initial publication or broadcast. CVM reviews these labeling and advertising materials to assess whether the materials contain only truthful, non-misleading information and provide risk and other information required to be included in these materials.

When CVM determines that promotional materials contain false or misleading information, the Center has several tools available to ensure compliance with the law, including achieving voluntary compliance through Untitled Letters and Warning Letters.

In Untitled Letters, CVM cites the violations found in the various labeling and advertisement pieces and asks sponsors to respond in writing to the cited violations, generally within 30 days. Similarly, in Warning Letters, CVM cites the violations found in the labeling and advertisement pieces. However, additional language is included indicating that CVM may take further regulatory or enforcement action against the sponsor. Also, sponsors are asked to reply in writing within 15 days of receipt of the Warning Letter, rather than the 30 days associated with Untitled Letters.

In October 2007, CVM began posting on its Web site violative promotional labeling and advertisement pieces along with the corresponding Untitled and Warning Letters to allow sponsors to review the original material that CVM objected to and learn from these examples.

Previously issued Untitled Letters can be found at *http://www.fda.gov/CVM/2007letters.htm* and Warning Letters at *http://www.fda.gov/foi/warning.htm*.

In 2007, CVM issued four Untitled Letters and five Warning Letters to sponsors in response to various labeling and advertisement violations. The letters principally cited either unsubstantiated claims or failure to include the required risk information.

Untitled Letters

In March 2007, CVM sent an Untitled Letter to a firm for overstating the effectiveness of its heartworm preventive product. The promotional piece suggested that the product was effective for the prevention, removal, and/or control of whipworms in dogs. However, the company had not provided evidence to support this claim of effectiveness.

In May 2007, CVM sent an Untitled Letter to a firm citing unsubstantiated safety claims and minimization of risks in several promotional labeling pieces for a canine non-steroidal anti-inflammatory drug (NSAID). The promotional pieces contained language implying that the product was safer, with respect to ulcers, than other currently approved canine NSAIDs. However, the firm had not provided evidence to support this claim. The promotional pieces also minimized the risks associated with product use. In particular, statements that communicated favorable information about the product were presented as large, bold headers, while the risk information was presented in a smaller, more difficult to read font. Because the risk was minimized, the product was considered misbranded.

In August 2007, CVM sent an Untitled Letter to a firm citing minimization of risk information and promotion of the drug for a new unapproved use. The promotional piece at issue contained statements that promoted an unapproved, more frequent product dosing regimen. Because the product was not approved for the stated dosing regimen, the product was rendered unsafe and adulterated. The promotional piece also omitted important risk information, thus causing the product to be misbranded.

And, in October 2007, CVM issued an Untitled Letter to a firm citing several violations: promoting a new unapproved use, omitting risk information, overstating the product's effectiveness, and using labeling that did not conform to the approved product labeling. Three promotional pieces for an equine dewormer promoted a new unapproved use: once every-other-month, year-round product use for protection of horses from tapeworms and other parasite infections. Because the product was not approved for every-other-month, year-round use in horses, the product was considered unsafe and adulterated. The product packaging associated with the new unapproved use also rendered the product unsafe and adulterated because it did not conform to the approved product labeling. All three pieces also omitted risk information regarding oral swelling and irritation found in the "Post-Approval Experience" section of the approved labeling. That omission caused the product to be misbranded. Furthermore, one piece contained statements implying 100 percent effectiveness against certain worm species and stating that no rotational use in conjunction with other

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FDA Proposes Reauthorization of User Fees for Pioneer Drugs and Authorization of the First-Ever User Fees for Generic Drugs

by Jon F. Scheid, Editor

The Food and Drug Administration sent proposals to Congress April 23 for the reauthorization of the user fee program for "pioneer" animal drugs and for the first-ever generic user fee program for generic animal drugs.

The proposed program for pioneer drugs would generate an estimated $98 million in user fees over 5 years, with $15.2 million collected in FY 2009, the first year of reauthorization of the program.

The proposed generic drug program would generate an estimated $27 million in user fees over 5 years, with $4.8 million collected in FY 2009, the first year of the program.

The user-fee revenue would supplement appropriated funding for animal drug review and associated activities.

User fees for pioneer drugs

Congress first approved the user fee program for pioneer drugs under the Animal Drug User Fee Act (ADUFA) of 2003.

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dewormers was needed. Because the firm did not provide evidence to support the claims, the product was considered misbranded.

In each of the four Untitled Letters, CVM asked the sponsors to immediately cease dissemination of the violative materials and to officially respond within 30 days regarding their intent to comply with CVM's requests.

Warning Letters

In June 2007, CVM sent a Warning Letter to a firm citing the minimization of risk associated with the use of the drug and failure to reveal material facts about the product in a television ad. In this case, the product also contained a "Boxed Warning," sometimes referred to as a "Black Box" warning. The television advertisement inadequately communicated the risks associated with the use of the product. Specifically, the advertisement failed to communicate the information in the Boxed Warning, thereby minimizing the risks associated with the product and misleadingly suggesting that the product is safer than had been demonstrated.

In addition, the letter cited the firm for failing to reveal relevant risk information in a non-broadcast promotional labeling piece. The Warning Letter cited the absence of adequate information regarding risks, which could result in the unsafe use of the product.

CVM sent three Warning Letters in June 2007 to firms for overstating their products' effectiveness claims. In one case, an advertisement for a canine heartworm preventive implied that use of the product would prevent transmission of zoonotic disease to humans. The company, however, had not provided any effectiveness data or clinical experience to support this claim. In the second case, an advertisement for a different canine heartworm preventive product suggested that the product was effective for the prevention, removal, and/or control of whipworms, but the company had not provided any evidence to support this claim of effectiveness. In the third case, various advertisements and labeling failed to reveal that the effectiveness data for the drug was the result of using the drug in conjunction with a behavior modification plan, as indicated on the approved label. These pieces were misleading because they suggested that the drug was more effective than had been demonstrated.

In July 2007, CVM sent a Warning Letter to a firm for both overstating the effectiveness of a drug and promoting a new unapproved intended use. The promotional piece at issue contained unsubstantiated effectiveness claims, suggesting that the Veterinary Feed Directive status of the drug related to its long-term effectiveness. Furthermore, the drug was promoted as being able to significantly increase average daily weight gain in pigs. Because the product was not approved for use in increasing average daily weight gain in pigs, the product was considered unsafe and adulterated.

In each of the five Warning Letters, CVM asked the sponsors to officially respond in writing within 15 days to the cited issues, stop dissemination of the violative pieces, and propose corrective actions. In some cases, CVM requested that the company include a comprehensive plan of action to disseminate a truthful, non-misleading, and complete corrective message about the issues discussed in the letter.

Conclusion

Because of the potential impact on the safe use of animal drugs, CVM takes false or misleading labeling and advertising seriously. Regulatory tools including Untitled and Warning Letters help CVM obtain voluntary compliance. Posting the letters on the Web provides a learning example to all companies involved in promoting animal drugs.

Several Firms, Corporate Executives Indicted in Adulterated Pet Food Case

by Walt D. Osborne, M.S., J.D., Assistant Editor

Two Chinese nationals and the businesses they operate, along with a U.S. company and its president and chief executive officer, were indicted on February 6, 2008, by a Federal grand jury in separate but related cases. The indictments follow an investigation by the Food and Drug Administration's Office of Criminal Investigations and are based on the roles the firms and the individuals played in a scheme to import products purported to be wheat gluten into the United States that were contaminated with melamine and related compounds, cyanuric acid, ammeline, and ammelide, the combination of which can cause kidney failure in animals.

The melamine-contaminated products are potentially associated with many illnesses and deaths of dogs and cats last year.

Wheat gluten is extracted from wheat and dried to yield a powder of high protein content. Pet food manufacturers use wheat gluten as a binding agent in the manufacture of certain types of pet food to thicken pet food "gravy."

The criminal indictments were filed by the U.S. Attorney's Office in Kansas City, MO, because the port of entry for the purported wheat gluten into the United States was a Kansas City warehouse. The indictments allege that more than 800 tons of purported wheat gluten, valued at nearly $850,000, was imported into the United States between November 6, 2006, and February 21, 2007. Melamine can artificially inflate the crude protein content of food additives, allowing exporters to pass ingredients of cheaper quality and price as more expensive ingredients, according to the indictment. Melamine and its related compounds have no approved use as ingredients in human or animal food in the United States.

Beginning in March 2007, pet food manufacturers recalled more than 150 brands of dog and cat foods after reports that animals had suffered kidney failure. Consumers and veterinarians have since reported many more illnesses and deaths potentially associated with these pet foods.

Multi-count indictments

One of the indictments charges the following Chinese firms and individuals with 26 felony counts:

- Xuzhou Anying Biologic Technology Development Co., LTD. (XAC), a Chinese firm that processes and exports plant proteins to the United States;
- Mao Linzhun, a Chinese national who is the owner and manager of XAC;
- Suzhou Textiles, Silk, Light Industrial Products, Arts and Crafts I/E Co. LTD. (SSC), a Chinese export broker that exports products from China to the United States; and
- Chen Zhen Hao, president of SSC and a Chinese national.

The indictment alleges that these Chinese firms and individuals, with the

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FDA Proposes Reauthorization of User Fees... *(Continued)*

FDA considers the program to be a success. ADUFA established a framework of sustained revenue through appropriations and user fees for sustained performance of the animal drug review program. When ADUFA was implemented, FDA set performance goals, including timeframes for drug reviews that were shortened each year of the 5-year ADUFA program. The additional funding helped FDA's Center for Veterinary Medicine meet those performance goals, including the deadlines for timely drug application review.

The proposal for ADUFA reauthorization would maintain the FY 2008 review timeframe goals. In addition, the proposal would begin a new process of "end review amendments," aimed at reducing the number of times a drug sponsor must resubmit an application for review due to the fact that CVM needed additional information to complete the review. The proposal would also establish processes to enhance communication between FDA and the animal drug industry, and it calls for the development of an electronic submission tool for industry submissions and online review.

The first (current) ADUFA program will sunset on October 1, 2008. The reauthorization would extend the program until the end of FY 2013.

Generic drug user fees

FDA believes that the availability of generic animal drugs gives consumers safe, effective, and lower cost alternatives to the pioneer drugs. Congress gave FDA the authority to evaluate and approve acceptable generic drugs in 1988 under the Generic Animal Drug and Patent Term Restoration Act.

The proposal for the generic user fee program, contained in the proposed Animal Generic Drug User Fee Act (AGDUFA), would establish timeframe goals for FDA review of generic drug applications. In addition, CVM would implement programs to enhance its communication with industry.

Understanding Genetic Variability in Dogs and Its Potential Role in Drug Development

by Michele Sharkey, D.V.M.; Marilyn Martinez, Ph.D.; Sanja Modric, D.V.M., Ph.D.; Lisa Troutman, D.V.M., MS; and Lynn Walker, D.V.M.; Office of New Animal Drug Evaluation

Veterinary medicine is in the early stages of understanding how genetic differences in animals can affect the way drugs work. This field of pharmacogenomics offers promise in veterinary medicine, as it does in human medicine. Researchers at the Center for Veterinary Medicine's Office of Research have begun studies in pharmacogenomics to determine when genetic tests can be used to determine drug safety in specific breeds of dogs. The Office of Research's work is being carried out under the Food and Drug Administration's Critical Path Initiative, which is designed to help move appropriate medical innovations that are safe and effective out of the laboratories to where they can help human and animal patients.

Background

In March 2004, FDA launched the Critical Path Initiative in an effort to stimulate and modernize the processes through which FDA-regulated products are developed, evaluated, and manufactured. To meet the Critical Path objectives, FDA plans to apply relevant disciplines (e.g., physiology, pharmacology, clinical pharmacology, and pharmacogenomics) and to identify ways to better correlate laboratory-generated data to clinical outcomes when the drug is administered to the broader population.

As part of the Critical Path Initiative, novel biomarkers may be identified that will serve as tools for ensuring the safe and effective use of products in either human or veterinary patients. Pharmacogenomics can be used as a tool to help identify novel biomarkers or physiological characteristics that impact a patient's drug response, both in human and veterinary medicine. Knowledge and understanding of genetic variability in drug response is critical because clinical testing may not always detect rare but important safety problems or the sample size is too small to detect trends that can occur in the broader population.

The Critical Path Initiative evolving

The Critical Path Initiative is one of FDA's top priorities. "It is fostering strong, sustained scientific advances that will enhance the health and well-being of all Americans," said Dr. Andrew von Eschenbach, Commissioner of Food and Drugs.

As part of its effort under the Critical Path Initiative, FDA is striving to obtain better information throughout the entire drug development process in an effort to improve the predictability of product clinical performance. A component of that effort is the identification of patient characteristics for which a drug might pose an unacceptable risk.

For example, concentrations of a drug in blood may be markedly affected by body condition, such as obesity. The degree of obesity was recently suggested as a major determinant of moxidectin kinetics in dogs, because obesity modulates the volume of distribution and, therefore, terminal half-life[1] of the drug. Similar results were reported with moxidectin in swine with different body condition[2].

With the objective of obtaining better information, CVM has launched two initiatives to address some of these scientific hurdles as they pertain to the veterinary profession. Those two initiatives—CVM's recent collaborative research on drug transporters, specifically P-glycoprotein (P-gp), and breed effects as they influence product safety and effectiveness in certain breeds of dogs—are discussed in this article. Both of these efforts have resulted in recent publications[3,4].

Advancing veterinary drug development

Pharmacogenomics is the study of how genetic variation in animals influences the safety and effectiveness of drug products administered to those animals. (This science is a rapidly evolving tool within human medicine, supporting efforts to improve the risk/benefit relationship of pharmacotherapy within the individual patient[5].)

Although there is a lack of genetic information in veterinary medicine, breed specific differences in response to endogenous substances (produced by the animal) and exogenous substances (from external sources) have been reported across a range of species, including cattle[6], sheep[7], chickens[8], and pigs[9].

With regard to dogs, there are more than 400 breeds recognized worldwide and 156 breeds recognized by the American Kennel Club. A consequence of the genetic selection associated with the propagation of breed-specific characteristics is a host of

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breed-related medical issues, which are recognized by the veterinary profession.

For example, specific metabolic diseases appear to follow breed lines. Human inborn errors of metabolism are generally attributable to several different mutations in a particular gene across a population of individuals, whereas in dogs (and cats) the same mutation is generally responsible for the specific disease within a breed[10]. While only 5 percent to 10 percent of human genetic variation has been shown to be associated with populations or races, 27 percent of genetic variation in dogs is associated with differences in breed[11].

Currently, there are more than 100 DNA-based tests for inherited diseases and traits in dogs. For example, a test is available to determine the presence of a multi-drug resistance gene 1 (MDR-1) mutation in dogs. The mutation results in nonfunctional P-gp. Dogs with nonfunctional P-gp show an increase in toxicity when administered certain P-gp substrates, such as ivermectin.[12,13] Considering the extensive research already generated by Dr. Katrina Mealey et al.[14] on the consequence of genetic mutations of the MDR-1 gene, CVM elected to focus on P-gp as a biomarker to enhance the evaluation of safe and effective new animal drugs.

P-gp and its role in therapeutics

P-gp is a transmembrane efflux (able to pump substances out of a cell) protein that affects the absorption, distribution, and elimination of certain drugs. It is part of a family of efflux transporters found in a variety of organs, including the intestine, the kidneys, the biliary system, and the central nervous system. P-gp provides the body with a mechanism to protect itself from potentially harmful substances by transporting substrates (e.g., across the intestinal tract [influx—pumping a substance in—and efflux], out of the brain, into the urine, and into the bile).

In 2001, Dr. Katrina Mealey reported a mutation in the MDR-1 gene that encodes for P-gp in dogs. The genetic mutation, believed to have first evolved in England in the late 1800s, creates a nonfunctional fragment of the original P-gp protein molecule. While the genetic defect has been commonly seen in herding breed dogs, it has also been found in some hounds.

Ivermectin sensitivity, a result of the nonfunctioning P-gp protein molecule, is most commonly reported in Collies; the MDR-1 mutation is postulated to affect 30 percent to 50 percent of the Collie population[15,16]. Sporadic descriptions of ivermectin sensitivity have been reported in other breeds, including Shetland Sheepdogs, Australian Shepherds, and Old English Sheepdogs.

Dogs (like humans) have two alleles for each trait. These alleles can be dominant or recessive.

Dogs can have one of three possibilities for the MDR-1 mutation. They can be homozygous recessive (in which case the MDR-1 alleles are mutant/mutant), heterozygous (with normal/mutant alleles), or wild-types (normal/normal alleles).

Because P-gp is an important efflux transporter of a wide range of compounds, dogs homozygous recessive for the MDR-1 mutation (mutant/mutant) have nonfunctioning P-gp, and therefore may have altered pharmacokinetic and toxicity profiles for P-gp substrates, including avermectins. In that case, avermectins accumulate in the brain, resulting in the dogs exhibiting clinical signs of neurotoxicity, such as ataxia, convulsions, vomiting, salivation, and tremors. The resulting neurotoxicity is dose-dependent and can be fatal.

In addition to neurotoxicity due to the macrocyclic lactones (ivermectin, moxidectin, milbemycin, and selamectin), dogs homozygous for the MDR-1 defect have been reported to exhibit signs of toxicity from other drugs at doses used without side effects in MDR-1 wild-type (normal/normal) dogs. For example, MDR-1 (mutant/mutant) dogs have exhibited neurotoxicity with standard doses of loperamide, a drug that is normally excluded from the brain by P-gp[17]. Dogs homozygous for the MDR-1 mutation have also been reported to have increased sensitivity (pronounced and protracted central nervous system depression) to acepromazine and butorphanol[18]. Altered biliary and/or renal excretion of vincristine and doxorubicin was proposed to cause myelosuppression and gastrointestinal tract toxicosis in a MDR-1 (mutant/mutant) Collie[19]. Similarly, digoxin toxicity was also documented in an MDR-1 (mutant/mutant) Collie[20].

P-gp can also impact canine medicine in ways unrelated to the MDR-1 mutation. For example, the failure of prednisolone to successfully treat naturally occurring chronic canine enteropathies in various dog breeds could be predicted by the over-expression of P-gp in the dog's lamina propria lymphocytes during steroid exposure[21]. In these animals, the diseased tissues effectively became resistant to steroid therapy. Accordingly, the question may not only be related to the integrity of a patient's P-gp function, but it could also have to do with whether a drug is a potential P-gp substrate or inhibitor.

Considering the importance of P-gp in modulating drug transport, CVM has safety concerns for other P-gp substrates. Therefore, CVM is examining some of the available technologies that can be used to screen for P-gp substrates, particularly with respect to predicting drug toxicity in P-gp deficient dogs.

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Understanding Genetic Variability . . . *(Continued)*

Ongoing research efforts

- **CANINE GENETIC TESTING:** A DNA test for the presence of the MDR-1 mutation is commercially available through Washington State University. Studies have yet to confirm that this test is sensitive or specific for ivermectin sensitivity.

  Nevertheless, the test does allow veterinarians to screen dogs for the MDR-1 mutation. Dogs heterozygous for this mutation may also be at risk. Initial information suggests that for some substrates, there may be compromised P-gp function in the heterozygous animal[22]. An understanding of the potential consequences of the MDR-1 genetic defect on drug pharmacokinetics should improve the ability to predict potential safety and effectiveness concerns in dogs carrying this mutation.

- **FDA/CVM'S CRITICAL PATH INITIATIVE:** FDA has recently approved a research proposal submitted by CVM's Office of Research under FDA's Critical Path Initiative to explore the potential impact of the MDR-1 gene mutation on drug safety and effectiveness. The research project will also explore methods for determining which drugs have safety and/or effectiveness profiles that may necessitate studies in dogs known to carry the mutation.

  Involving review scientists within CVM's Office of New Animal Drug Evaluation, the research program will initially address the potential differences in the pharmacokinetics of several known P-gp substrates when administered to dogs that are homozygous recessive, heterozygous, or wild-types for the MDR-1 mutation.

  Reliable screening procedures for identifying potential P-gp substrates, particularly those molecules at risk of crossing the blood-brain barrier in P-gp deficient dogs, are needed to help evaluate the safety of new drugs for use in dogs. Therefore, identifying alternative *in vitro* and *in vivo* tests that can serve as screening methods for detecting such P-gp substrates is needed. The Office of Research will also work on the development of an *in vitro* method for determining whether a compound is a P-gp substrate and if an *in vivo* transgenic knockout mouse model can serve as a reliable testing method.

Conclusion

Despite the current focus on P-gp, it is important to consider the overall objectives of the Critical Path Initiative to identify physiological variables, genetic screens, or novel biomarkers that can be used to improve the safety and effectiveness data generated from small studies.

Similar to human medicine, the genetic variations present within veterinary species can affect drug safety and effectiveness. However, veterinary medicine is in the early stages of understanding the role of pharmacogenomics in drug response. Information relating to P-gp deficiencies in dogs can serve as a starting point upon which veterinary scientists build a pharmacogenomic database. Ultimately, the goal is to utilize information derived not only in dogs but across all species, to better understand population variability, test for sources of this variability, and minimize the risk of adverse drug reactions in veterinary species.

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Escherichia Coli O157:H7 Foodborne Illness and the Usefulness of the Critical Path in FDA's Work to Combat It

by Richard Arkin, J.D., Assistant Editor

Under the Food and Drug Administration's Critical Path Initiative, the Center for Veterinary Medicine is working as part of a joint effort of industry and government agencies to identify key problems and develop targeted solutions to reduce or eliminate *Escherichia coli* O157:H7 in or on cattle going to slaughter.

E. coli O157:H7 is a strain of the commonly found bacterium that has emerged as a significant cause of foodborne illness in the United States. *E. coli* strains are commonly found in the lower intestines of healthy humans and other warm blooded animals, such as mammals and birds. Most strains are harmless and are part of normal gut flora. They benefit their hosts by producing vitamin K3 or blocking the growth of pathogenic bacteria in the intestine.

E. coli O157:H7 (the letters and numbers in the name refer to the specific markers found on organisms surfaces that distinguish this strain from others) is just one of hundreds of *E. coli* strains. *E. coli* O157:H7 is not pathogenic in cattle and is readily carried in the intestinal tract of healthy animals. Unlike most other strains, however, this one produces a toxin that can cause a severe infection in humans, resulting in serious food poisoning. It is enterohemorrhagic in humans, which means it can cause bloody diarrhea, which occasionally leads to kidney failure, particularly in children, the elderly, and those who are immuno-compromised.

The E. coli *Coalition*

In 2006, CVM and the National Cattlemen's Beef Association (NCBA), a cattle producers' organization,

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Understanding Genetic Variability . . . *(Continued)*

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Escherichia Coli O157:H7 . . . *(Continued)*

joined together to form the *E. coli* Coalition. Additional members—the U.S. Department of Agriculture (USDA), the American Meat Institute (AMI), and the Animal Health Institute (AHI)—have since joined.

The coalition has identified four areas of focus as part of its "Farm to Fork" approach:

- Pre-harvest interventions (on the farm)
- Transport (from the farm to arrival at the slaughter plant)
- Post-harvest (from the slaughter plant to the finished/packaged product)
- Environmental impact

CVM is working with other members of the group on the pre-harvest frame, trying to identify therapeutic interventions to reduce or eliminate *E. coli* O157:H7 in or on cattle presented for slaughter. FDA is collaborating with USDA's Animal and Plant Health Inspection Service's Center for Veterinary Biologics, NCBA, and AHI on establishing standards for product effectiveness. These standards will utilize tools available under FDA's Critical Path Initiative, while still being acceptable under FDA's authorizing statutes.

Most *E. coli* illness in the United States has been associated with eating undercooked, contaminated ground beef. The number of *E. coli* organisms required to cause disease in humans is not known; it is suspected to be small. Meat becomes contaminated by *E. coli* from cattle intestines during slaughter and the *E. coli* organisms can be thoroughly mixed into beef when it is ground. Contaminated beef generally looks and smells normal.

Meat becomes contaminated by E. coli from cattle intestines during slaughter and the E. coli organisms can be thoroughly mixed into beef when it is ground.

E. coli illness can also occur because bacteria present on a cow's udder or on equipment gets into raw milk consumed without pasteurization.

Consumers can prevent *E. coli* O157:H7 infection by thoroughly cooking ground beef, avoiding unpasteurized milk, using safe food preparation techniques, and washing hands frequently and carefully.

E. coli O157:H7 was first recognized as a pathogen as a result of an outbreak of unusual gastrointestinal illness in 1982. The illness was similar to other outbreaks in the United States and Japan, and this incident was traced to contaminated hamburger. The O157:H7 serotype of *E. coli* was recognized by the Centers for Disease Control and Prevention (CDC) as the causative agent of the illness in two separate outbreaks of hemorrhagic colitis in Michigan and Oregon in 1982. This serotype was then rare, having been first isolated in 1975.

Because the organism is common in the intestines of healthy cattle, preventive measures on cattle farms and during meat processing are being investigated by Coalition members.

NCBA, along with AMI, AHI, and other trade groups, has been working on a number of control point interventions to resolve the specific problem of *E. coli* O157:H7. FDA is aware that the NCBA and other groups are diligently searching for on-farm interventions by funding research to identify therapeutic interventions. The agency has concluded, however, that no single intervention is likely to eliminate the *E. coli* 0157:H7 problem.

Critical Path Initiative

Under FDA's Critical Path Initiative, developed to facilitate the evaluation and approval process, FDA and CVM are also working to combat the problem by research and by speeding evaluation and approval of therapeutic interventions for *E. coli* O157:H7.

FDA knows that the current medical product development path has become increasingly challenging, inefficient, and costly, and that costs of product development have soared over the last decade or so. The Agency also recognizes that the increasing costs and growing difficulties of medical product development lead to stagnation and decline in innovation, which could mean that the biomedical revolution of recent years might not deliver on its promise of better health.

At FDA, the Critical Path Initiative is seen as a way to identify and prioritize the most pressing development problems and the areas that provide the greatest opportunities for rapid improvement and public health benefits. It is FDA's management tool for the scientific process by which a potential human or animal drug, biological product, or medical device is transformed from discovery or "proof concept" into a medical product.

The Critical Path Initiative allows the Agency flexibility in mapping out the regulatory path to market for new and innovative therapeutics. It utilizes the newest scientific tests and tools to predict whether a product candidate will be safe and effective. These tools can predict which product candidates do not hold

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Escherichia Coli O157:H7 . . . *(Continued)*

Escherichia coli O157:H7 and Disease

The Centers for Disease Control and Prevention (CDC) has recognized four classes of enterovirulent *Escherichia coli* that cause gastroenteritis in humans. CDC refers to these as the EEC Group. Among these is the enterohemorrhagic strain designated *E. coli* O157:H7.

E. coli normally is present in the intestines of all animals, including humans. When certain culture methods are used in the laboratory, *E. coli* is the predominant species found in feces. *E. coli* usually serves a useful function in the body by synthesizing vitamins and suppressing the growth of harmful bacterial species.

Some varieties of *E. coli* strains are capable of causing human illness by several different mechanisms. The O157:H7 serotype of *E. coli* is a rare strain that produces large quantities of one or more potent toxins that cause severe damage to the intestinal lining. These toxins are closely related or identical to the toxin produced by *Shigella dysenteriae*, one of the causes of dysentery.

E. coli O157:H7 causes the acute disease called hemorrhagic colitis. The illness is characterized by severe abdominal cramping and pain, as well as watery diarrhea that usually becomes very bloody. Vomiting sometimes also occurs. Generally, there is either no fever or a low-grade fever.

According to CDC, all people are believed to be susceptible to hemorrhagic colitis, but young children and the elderly appear to progress to more serious symptoms more frequently. Some victims, particularly the very young, have developed the hemolytic uremic syndrome (HUS), characterized by renal failure and hemolytic anemia. HUS, which can result in permanent loss of kidney function, can affect as many as 15 percent of hemorrhagic colitis victims. HUS, plus two other symptoms, fever and neurologic symptoms, constitutes thrombotic thrombocytopenic purpura (TTP), which can be found in some elderly victims. TTP can have a mortality rate in the elderly as high as 50 percent.

According to CDC, outbreak data and the known ability of the organism to be passed from person to person in nursing homes, day-care centers, and other personal care facilities, indicate that the presence of as few as 10 organisms could result in disease.

Hemorrhagic colitis is diagnosed by laboratory isolation of the causative agent in diarrheal stools. Confirmation can come from isolation of *E. coli* of the same serotype from the food believed to have caused the illness.

CDC reports that hemorrhagic colitis infections are not commonly identified, but that actual reported cases may not reflect the true frequency of the disease. CDC says that *E. coli* O157:H7 is thought to be the second most common cause of bacterial diarrhea (*Salmonella* is the most common cause) in the Pacific Northwest States. Victims with the most severe cases, who have profuse, visible blood in their diarrhea, probably seek medical attention. However, CDC believes that less severe cases in which blood may be less visible, or may not be present at all, are probably more numerous.

promise early in the development process, thereby allowing sponsors to direct resources to products more likely to meet safety and efficacy requirements.

Through the Critical Path, FDA brings national focus to current product development issues, serving as a hub for problem identification and information exchange. FDA encourages use of Critical Path tools by accepting the results of the new tools as valid proof in product review (including updated science-based standards and guidances). FDA also serves as the catalyst to initiate projects and collaborations to help modernize the Critical Path.

One of the key areas of focus for the Critical Path at FDA is bringing to market products to address urgent public health needs. As part of this process, FDA is interested in working with sponsors to identify and bring to market interventions. A therapeutic intervention just prior to slaughter, in conjunction with other risk management interventions during the slaughter and processing of beef, would reduce the exposure of humans to *E. coli* O157:H7. This reduction would be an opportunity for a direct public health benefit through the Critical Path, so the *E. coli* initiative has given CVM an identified project under the Critical Path at FDA, as well as giving the Center a clearly defined role in efforts to reduce *E. coli* O157:H7.

CVM sees the Critical Path as a mechanism for expedited review of potentially approvable products, while products that cause human food safety, target animal safety, environmental or resistance concerns will not qualify for Critical Path expedited review.

CVM wants to learn about research involved in new technologies to address the *E. coli* O157:H7 problem

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Escherichia Coli O157:H7 . . . *(Continued)*

and is interested in working with sponsors of animal drugs in a cooperative approach to finding new therapeutic interventions.

The Center wants to allow those technologies to come to market that have the most chance of becoming therapeutic interventions to eliminate *E. coli* O157:H7 prior to slaughter and thus reduce or eliminate foodborne illness caused by this bacterium. The Critical Path is an important element in achieving this goal.

How the Consumer Can Fight Foodborne Illness

The Centers for Disease Control and Prevention (CDC) recommendations for prevention of an infection caused by *Escherichia coli* O157:H7 include:

- Cook all ground beef or hamburger thoroughly. Make sure that the cooked meat is gray or brown throughout (not pink), any juices run clear, and the inside is hot.
- The temperature of the meat should reach a minimum of 160 degrees F, as measured with a digital instant-read meat thermometer.
- If you are served an undercooked hamburger in a restaurant, send it back.
- Consume only pasteurized milk and milk products. Avoid raw milk.
- Consume only pasteurized juices and ciders.
- Make sure that infected persons, especially children, wash their hands carefully and frequently with soap and water to reduce the risk of spreading the infection.
- Drink municipal water that has been treated with adequate levels of chlorine, or other effective disinfectants.
- Avoid swallowing lake or pool water while swimming.
- Wash hands thoroughly after using the toilet.
- People with diarrhea should not:
  - swim in public pools or lakes
  - bathe with others
  - prepare food for others.

Using FoodNet for Surveillance of *E. coli* bacteria

An estimated 73,000 cases of infection and 61 deaths occur each year in the United States from *Escherichia coli* O157:H7, and this strain has been responsible for a number of costly product recalls. As a result, FDA has become part of a multi-agency foodborne surveillance initiative, the Foodborne Diseases Active Surveillance Network (FoodNet), to protect human health by combating *E. coli* O157:H7.

The other agencies involved are the Centers for Disease Control and Prevention (CDC), the U.S. Department of Agriculture's (USDA's) Food and Nutrition Service and the Center for Veterinary Biologics.

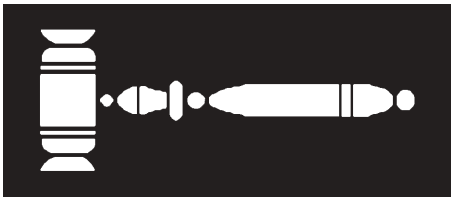
FoodNet, described in detail last year in Volume XXII No. VI of *FDA Veterinarian*, is a collaborative project of the FDA, CDC, USDA, and State public health laboratories. The project consists of active surveillance for foodborne diseases and related studies designed to help public health officials better understand the epidemiology of foodborne diseases in the United States.

FoodNet sites around the country employ a sampling scheme in which at least one grocery store each month is visited. Personnel from each site purchase 10 packages each of retail chicken breasts, pork chops, ground turkey, and ground beef from the retail outlets.

At each of 10 State public health laboratories, a "rinse" (liquid sample for laboratory analysis) is produced using standardized methods from each meat sample for the presence of *Salmonella* and *Campylobacter*. The rinses are produced using procedures adapted from the FDA's *Bacteriological Analytical Manual*, which presents the agency's preferred laboratory procedures for microbiological analyses of foods and cosmetics.

Isolates are sent to the Office of Research at the Center for Veterinary Medicine's laboratories for identification, antimicrobial susceptibility testing, and genetic studies. In addition, four sites (Georgia, Maryland, Oregon, and Tennessee) culture the rinses for *E. coli* and *Enterococcus* and send the isolates on to CVM.

Regulatory Activities – February 2008



Warning Letters

A WARNING LETTER was issued by FDA to Aaron G. Poupore, co-owner/herdsman of the Papas Dairy, LLC, North Bangor, NY, for violations of the adulteration provisions of the Federal Food, Drug, and Cosmetic Act (FFDCA). Specifically, the dairy sold a cow for slaughter as food that contained residues of 0.60 parts per million (ppm) of the drug sulfadimethoxine in the liver tissue and 0.41 ppm of the same drug in the muscle tissue. A tolerance of 0.1 ppm of this drug in the uncooked edible tissues of cattle has been established by FDA (21 CFR 556.640), rendering the animal adulterated under Section 402(a) of the Act. In addition, the firm was cited for violating Section 501(a) of the Act for failing to use the drugs Albion (sulfadimethoxine boluses) and Penicillin G Procaine in conformance with their approved labeling. The WARNING LETTER also cited the dairy for failing to maintain adequate treatment records.

Francis H. Roderick of Old Carolina Farms, Ijamsville, MD, has received a WARNING LETTER for violations of Section 402(a) of the FFDCA. The firm consigned a bob veal calf for slaughter as food that was found to contain residues of the drug sulfamethazine in the liver tissue at 131.89 ppm and in the muscle tissue at 179.88 ppm. FDA has set a tolerance for this drug of 0.1 ppm (21 CFR 556.670), rendering the animal adulterated. In addition, the firm was cited for providing a false guaranty to FDA in violation of Section 301(h) of the Act, and for failing to use sulfamethazine in conformance with its approved labeling in violation of Section 501(a) of the Act. And, according to the WARNING LETTER, the firm lacked an adequate system to ensure that animals medicated have been withheld from slaughter for appropriate periods of time to permit depletion of potentially hazardous residues of drugs from edible tissues.

FDA issued a WARNING LETTER to Dale L. Utter, owner of the Piedmont Dairy, Moore, SC, for violation of the adulteration provision in Section 402(a) of the FFDCA. Specifically, the firm sold a dairy cow for slaughter as food that was found to have penicillin in the kidney tissues at 7.03 ppm, in the liver tissue at 0.37 ppm, and in the muscle tissue at 0.20 ppm. FDA has set a tolerance of 0.05 ppm for residues of penicillin in the edible tissues of cattle (21 CFR 556.510). As a result, the food was adulterated under Section 402(a). In addition, the firm had signed a certification, stating that the dairy was not delivering any livestock with illegal drug residues. Therefore, the firm was found to have provided a false guaranty pursuant to Section 301(h) of the FFDCA. Adequate treatment records were also found to be lacking.

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...Indicted in Adulterated Pet Food Case *(Continued)*

intent to defraud and mislead, delivered adulterated and misbranded food into interstate commerce.

Also indicted were ChemNutra, Inc., a Las Vegas, NV, corporation that buys food and food components from China to sell to U.S. companies in the food industry, along with ChemNutra owners Sally Qing Miller and her husband, Stephen S. Miller, who were charged in a separate, but related, 27-count indictment, listing 26 misdemeanor charges and 1 felony conspiracy charge. Sally Qing Miller, a Chinese national, is the controlling owner and president of ChemNutra; Stephen Miller is an owner and CEO of ChemNutra.

Both indictments charge all seven defendants with, among other things, causing the delivery of adulterated food that contained melamine, a substance which may render the food injurious to health, into interstate commerce and with causing the introduction of misbranded food into interstate commerce. ChemNutra and the Millers have also been charged with conspiring to defraud the companies that bought the purported wheat gluten.

ChemNutra contracted with SSC, a Chinese registered export broker, to purchase food grade wheat gluten, according to the indictment. SSC then entered into a separate contract with XAC to supply the wheat gluten it needed to fulfill its contract with ChemNutra.

Prison Terms and Fines May Be Imposed

The potential penalties differ, based on the charges and whether the defendant is a corporation or an individual. The misdemeanor counts faced by ChemNutra carry a fine of up to $200,000 per count, while the misdemeanor counts faced by the Millers carry fines of up to $100,000 and prison sentences of up to 1 year per count. The one felony count faced by ChemNutra and the Millers carries a fine of up to $500,000 for the corporation and fines of up to $250,000 and prison sentences of up to 5 years for the individuals. For the 26 felony counts faced by the Chinese corporations and individuals, the corporations face fines of up to $500,000 per count, and the individuals face fines of up to $250,000 and prison sentences of up to 3 years per count.

Regulatory Activities *(Continued)*

Similar violations of Section 402(a) of the FFDCA were cited in a WARNING LETTER issued by FDA to Mark Gullicksrud, president, and Gary L. Gullicksrud, vice president, of Hamlin Valley Farms, Strum, WI. Specifically, the firm consigned a cattle trucker to transport a dairy cow for slaughter as food. Inspection revealed the presence of ampicillin in the kidney tissue of the animal at 0.06 ppm. FDA has set a tolerance for this drug in the kidney tissue of cattle at 0.01 ppm (21 CFR 556.40), thereby rendering the food adulterated under Section 402(a). The firm was also found to have adulterated ampicillin within the meaning of Section 501(a)(5) of the FFDCA by failing to use the drug in conformance with the conditions for extralabel used prescribed by the firm's veterinarian. In addition, the firm provided a signed certification that stated that none of the animals it supplied contained illegal levels of drug residues, which proved to be untrue. Pursuant to section 301(h) of the Act, providing such a false guaranty is prohibited.

Fred, Scott and Trent Sherman, co-owners of the Sherman Dairy, Winton, CA, received a WARNING LETTER from FDA for offering an animal for sale for slaughter as food that was adulterated under Section 402(a) of the FFDCA. An analysis of tissue samples revealed the presence of penicillin in the kidney at 0.29 ppm; the tolerance set by FDA for penicillin in the edible tissues of cattle is 0.05 ppm (21 CFR 556.510). In addition, the firm adulterated AgriPharm PEN-AQUEOUS, Penicillin G Procaine, Injectable Suspension U.S.P. within the meaning of section 501(a)(5) of the Act when it failed to use the drug in conformance with its approved labeling. The drug was administered without following the dosage level set forth in the approved labeling and it was done without the supervision of a licensed veterinarian, in violation of 21 CFR 530.11 (a).

A WARNING LETTER was issued to William R. Scheenstra, president of Scheenstra Farms, Inc., of Sunnyside, WA, for violation of Section 402(a) of the FFDCA. The firm sold a dairy cow for slaughter as food that was found to have residues of ampicillin in the liver tissues at 0.04 ppm and in the kidney tissues at 0.70 ppm. FDA has set a tolerance for residues of this drug in the uncooked edible tissues of cattle at 0.01 ppm (21 CFR 556.40), rendering the animal in question adulterated under Section 402(a). FDA's investigation also revealed that the firm's extralabel use of ampicillin failed to comply with section 512(a) of the FFDCA and with 21 CFR Part 530. For example, the firm administered ampicillin for a condition (mastitis) not set forth in the approved labeling and it did so without the supervision of a licensed veterinarian, in violation of 21 CFR 530.11(a). Furthermore, the extralabel use resulted in an illegal drug residue.

Recalls

A Class II firm-initiated recall is ongoing by Durotec USA Co. of Vancouver, WA, for 7,000 units of UDDERCARE Washing Liquid and Organic Wash. The reason for the recall is that the product, which is used for teat wash for dairy cows, is contaminated with bacteria. Distribution occurred in Washington, California, and Oregon.

A total of 772 pails (Code DC-1499) and 240 pails (Code DC-1483) of Pharmacia & Upjohn Quartermaster Suspension, penicillin-dihydrostreptomycin in oil are the subject of an ongoing, firm-initiated Class II recall by Pfizer, Inc., New York, NY. The recall was begun because the products were out of specification. The products were distributed in Iowa, Colorado, Idaho, Nebraska, and Texas.

A firm-initiated Class II recall is ongoing by IVX Animal Health, Inc., of St. Joseph, MO, for approximately 141,000 vials of Ivermectin Liquid for Horses (10 mg per mL) in 100-mL and 200-mL vials. The recall was begun because a precipitate forms once the bottles have been opened. The products were distributed nationwide.

A Class III firm-initiated recall has been completed by CP Medical of Portland, OR, for 547 boxes of 12-each, Monofilament Polydioxanone Synthetic Absorbable (PDO), Sterile Suture (Violet Color) 0 (3.5 metric) 30″ (75 cm) 1/2 37 mm Taper. The recall was carried out because the monofilament sutures were incorrectly labeled; specifically, the package is labeled with suture size 0 but may contain suture size 3/0. The products had been distributed in Arizona, Louisiana, Massachusetts, Michigan, Missouri, North Carolina, Ohio, and Texas.

Comings and Goings

New Hires

OFFICE OF THE DIRECTOR

- Jacintha Tolson, Program Specialist

OFFICE OF RESEARCH

- Kathleen Orr, Program Support Specialist

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Jayne Tung, Veterinary Medical Officer

Departures

OFFICE OF THE DIRECTOR

- Stephen Sundlof, Center Director
- Anna Roy, Secretary

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Henry Ekperigin, Biologist

Approvals for February 2008

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

ZILMAX (zilpaterol hydrochloride), RUMENSIN (monensin), and TYLAN (tylosine phosphate) Type A medicated articles (NADA 141-276), filed by Intervet, Inc., Millsboro, DE. The NADA provides for the use of ZILMAX (zilpaterol hydrochloride), RUMENSIN (monensin), and TYLAN (tylosine phosphate) Type A medicated articles to make dry and liquid three-way combination Type B and Type C medicated feeds used for increased rate of weight gain, improved feed efficiency, and increased carcass leanness; also for prevention and control of coccidiosis due to *Eimeria bovis* and *E. zuernii*; and for reduction of incidence of liver abscesses caused by *Fusobacterium necrophorum* and *Arcanobacterium (Actinomyces) pyogenes* in cattle fed in confinement for slaughter during the last 20 to 40 days on feed. Notice of approval was published February 1, 2008.

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

REGUMATE (altrenogest) (NADA 131-310), filed by Intervet, Inc., Millsboro, DE. The supplemental NADA provides for a revised warning statement on the product labeling of REGUMATE (altrenogest), an oral solution administered to mares for suppression of estrus. Notice of approval published February 21, 2008.

Phenylbutazone Tablets (NADA 91-818 and NADA 94-170), filed by IVX Animal Health, Inc., St. Joseph, MO. The supplemental NADAs provide for revisions to the warning statements on the product labeling for the use of Phenylbutazone Tablets in horses and dogs. Notice of approval published February 13, 2008.

DRAXXIN (tulathromycin) Injectable Solution (NADA 141-244), filed by Pfizer, Inc., New York, NY. The supplemental NADA provides for treatment of infectious bovine keratoconjunctivitis associated with *Moraxella bovis* and the addition of a pathogen, *Mycoplasma hyopneumoniae*, to the indication for use for treatment of swine respiratory disease. Notice of approval published February 1, 2008.

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

PHOENECTIN (ivermectin) Liquid for Horses (ANADA 200-202), filed by IVX Animal Health, Inc., St. Joseph, MO. The supplemental ANADA provides for the addition of indications for use and minor revisions to the product labeling on ivermectin that conform to the pioneer product labeling. Notice of approval published February 21, 2008.

(Continued, next page)

Approvals for February 2008 *(Continued)*

Correction

The previous edition of *FDA Veterinarian* listed an approval for AVIAX II, but the listing incorrectly included the name SIMPLICEF. Here is the correct listing.

AVIAX II (semduramicin) (NADA 141-281), filed by Phibro Animal Health, Ridgefield Park, NJ. The NADA provides for the use of AVIAX II (semduramicin) Type A medicated article containing semduramicin (as semduramicin sodium biomass) to manufacture Type C medicated broiler chicken feed for the prevention of coccidiosis caused by *Eimeria tenella*, *E. acervulina*, *E. maxima*, *E. brunetti*, *E. necatrix*, and *E. mitis*. Notice of approval was published January 4, 2008.

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