Challenges and Issues in Veterinary Pharmacology and Animal Health 2004—Preface

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It is our pleasure to present the second theme issue of the *AAPS Journal* (formerly *AAPS PharmSci*) pertaining to veterinary pharmacology. Recognizing that our human health counterparts rarely have the opportunity to examine the activities affecting veterinary medicine, these theme issues represent an effort to enhance interdisciplinary communication.

Since publishing the first *AAPS PharmSci* veterinary theme issue in 2002, the Food and Drug Administration Center for Veterinary Medicine (CVM) has enjoyed numerous accomplishments. Between the year 2002 and July 2005, CVM published 43 guidance documents (Table 1). Sixteen of these guidance documents were written in collaboration with the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH), a trilateral (EAU-Japan-USA) program aimed at harmonizing technical requirements for veterinary product registration.¹

Another important accomplishment has been ratification of the Animal Drug User Fee Act of 2003 (ADUFA) which, similar to the Prescription Drug User Fee Act (PDUFA) authorizes the FDA to collect fees “for certain animal drug applications, and for the establishments, products and sponsors associated with these and previously approved animal drug applications, in support of the review of animal drugs.” These additional resources will support FDA/CVM’s efforts to fulfill its responsibilities under the Federal Food Drug and Cosmetic Act to ensure that new animal drug products are safe and effective for the target animal species and, when administered to food-producing animals, that conditions of use result in animal products that are safe for human consumption. This legislation is intended to help FDA expedite and improve its review of applications for new animal drugs so that safe and effective new products will be readily available.¹

On a somber note, CVM has needed to address public concerns regarding the December 2003 discovery of a cow in Washington State that was infected with Bovine Spongiform Encephalopathy (BSE). BSE is a new-variant of the associated human disease, Creutzfeldt–Jakob disease.² Creutzfeldt–Jakob disease (CJD) is a degenerative disease of the central nervous

system that is caused by infectious proteins called *prions*. CJD is a progressive disease presenting with dementia and myoclonus, usually resulting in death within a year of onset.³ This discovery resulted in the implementation of additional firewalls to protect the American public. Initially, the FDA implemented a final rule on August 4, 1997 that prohibits the use of most mammalian protein in feeds for ruminant animals (Title 21 Part 589.2000 of the *Code of Federal Regulations*). This rule includes the prohibition of certain feeding and manufacturing practices involving feed for cattle and other ruminant animals, namely prohibition of the use of most mammalian protein in feeds for ruminant animals. On January 26, 2004, Health and Human Services (HHS) Secretary Tommy G. Thompson announced several new public health measures to be implemented by the FDA in an effort to strengthen efforts to protect Americans from exposure to the agent thought to cause BSE.⁴⁻⁵ The FDA will publish two interim final rules that will take effect immediately upon publication. The first interim rule will ban the following materials from FDA-regulated human foods, dietary supplements and cosmetics:

- Any material from “downer” cattle (animals unable to walk).
- Any material from “dead” cattle (animals that die on the farm before reaching the slaughter plan).
- Specified risk materials that are known to harbor the highest concentrations of the infectious agents for BSE, such as the brain, skull, eyes and spinal cord of cattle 20 mo or older, and a portion of the small intestine and tonsils from cattle, regardless of their age and health status.
- The products known as mechanically separated beef, which may contain specified risk materials. An automated system for cutting meat off bones (Advanced Meat Recover) may be used since the USDA regulations do not allow the presence of specified risk materials in this product.

A second interim rule will further lower the risk that cattle will be purposefully or inadvertently fed prohibited proteins by implementing several specific changes:

- This rule will eliminate the present exemption in the feed rule that allows mammalian blood and blood products to be fed to other ruminants as a protein source.

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Table 1. Draft and Final Guidances Published Between 2002 and 2004*

Guidance Number	Title	Date Issued
52	Assessment of the Effects of Antimicrobial Drug Residues from Food of Animal Origin on the Human Intestinal Flora, February 18, 2004 pdf doc	02/18/04
80	Studies to Evaluate the Utility of Anti-Salmonella Chemical Food Additives in Feeds pdf doc	11/21/02
82	Guidance for Industry: Development of Supplemental Applications for Approved New Animal Drugs—Final Guidance pdf doc	10/28/02
107	How to Use E-Mail to Submit a Protocol to the Center for Veterinary Medicine	03/27/03
110	Guidance for Industry No. 110: Effectiveness of Anthelmintics: Specific Recommendations for Porcine—VICH GL16—Final Guidance pdf doc	06/27/02
111	Guidance for Industry No. 111: Effectiveness of Anthelmintics: Specific Recommendations for Canine—VICH GL19—Final Guidance pdf doc	06/27/02
113	Guidance for Industry: Effectiveness of Anthelmintics: Specific Recommendations for Feline—VICH GL20—Final Guidance doc pdf	06/19/02
114	Guidance for Industry: Effectiveness of Anthelmintics: Specific Recommendations for Poultry-Gallus Gallus—VICH GL21—Final Guidance doc pdf	06/19/02
115	Guidance for Industry: Safety Studies for Veterinary Drug Residues in Human Food: Reproduction Studies—VICH GL22—Final Guidance doc pdf	01/03/02
116	Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Genotoxicity Testing—VICH GL23—Final Guidance doc pdf	01/03/02
118	Guidance for Industry: Mass Spectrometry for Confirmation of the Identity of Animal Drug Residues—Final Guidance doc pdf	05/01/03
119	Guidance for Industry and Reviewers No. 119: How the Center for Veterinary Medicine Intends to Handle Deficient Submissions Filed During the Investigation of a New Animal Drug doc pdf	08/29/02
122	Guidance for Industry No. 122: Manufacture and Labeling of Raw Meat Foods for Companion and Captive Noncompanion Carnivores and Omnivores—Draft doc pdf	12/12/02
132	Guidance for Industry: The Administrative New Animal Drug Application Process—Draft doc pdf	11/06/02
143	CVM Guidance for Industry No. 143: Pharmacovigilance of Veterinary Medicinal Products: Controlled List of Terms—VICH GL30—Draft Guidance doc pdf FR Notice	02/01/02
144	Guidance for Industry: Pre-Approval Information for Registration of New Veterinary Medicinal Products for Food-Producing Animals With Respect to Antimicrobial Resistance—VICH GL27—Draft Guidance doc pdf	06/12/03
147	Guidance for Industry No. 147: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-Day) Toxicity Testing—VICH GL31 doc pdf	11/12/03
148	Draft Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing—VICH GL32 doc pdf	08/29/02
149	Draft Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing—VICH GL33 doc pdf	08/29/02
150	Guidance for Industry: Status of Clove Oil and Eugenol for Anesthesia of Fish pdf doc	06/11/02
151	Guidance for Industry: FDA Export Certificates htm pdf	08/08/02
152	Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs With Regard to Their Microbiological Effects on Bacteria of Human Health Concern doc pdf	10/23/03
153	Draft Guidance for Industry: Drugs, Biologics, and Medical Devices Derived From Bioengineered Plants for Use in Humans and Animals	09/02
156	Draft Guidance for Industry: Comparability Protocols?Chemistry, Manufacturing, and Controls Information; Availability pdf doc	02/03
157	Guidance for Industry: Part 11, Electronic Records, Electronic Signatures—Scope and Application doc pdf	08/03
158	Guidance for Industry: Use of Material From Deer and Elk in Animal Feed doc pdf	09/15/03
159	Guidance for Industry No. 159: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI—VICH GL-36 doc pdf	02/10/05
160	Guidance for Industry: Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing—VICH GL-37 doc pdf	02/07/05

Table 1 (Continued). Draft and Final Guidances Published Between 2002 and 2004*

Guidance Number	Title	Date Issued
162	Draft Guidance for Industry: Comparability Protocols—Protein Drug Products and Biological Products—Chemistry, Manufacturing, and Controls Information pdf	09/03
163	Draft Guidance for Industry: Formal Dispute Resolution?Scientific and Technical Issues Related to Pharmaceutical CGMP doc pdf	08/03
164	Guidance for Industry: PAT?A Framework for Innovative Pharmaceutical Manufacturing and Quality Assurance doc pdf	09/04
165	Draft Guidance for Industry: Providing Regulatory Submissions in Electronic Format—General Considerations doc pdf	10/03
166	Draft Guidance for Industry #166 - Environmental Impact Assessments (EIA's) for Veterinary Medicinal Products (VMP's) - phase II - VICH GL38 pdf doc	04/20/04
167	Guidance for Industry: Prior Notice of Imported Food Questions and Answers	12/12/03
168	Guidance to Industry: Prior Notice of Imported Food: Harmonized Tariff Schedule Codes Flagged With Prior Notice Indicators	11/20/03
169	Guidance for Industry: Drug Substance?Chemistry, Manufacturing, and Controls Information, Draft Guidance pdf doc	01/04
170	Guidance for Industry: Animal Drug User Fees and Fee Waivers and Reductions, Final Guidance, March 15, 2004 html pdf	3/15/04
171	Draft Guidance for Industry - Waivers of In Vivo Demonstration of Bioequivalence of Animal Drugs in Soluble Powder Oral Dosage Form Products and Type A Medicated Articles, August 2004 doc pdf	8/04
173	Guidance for Industry - Animal Drug Sponsor Fees under the Animal Drug User Fee Act (ADUFA), Draft Guidance doc pdf <i>Appendix</i> pdf doc	02/07/05
174	Guidance for Industry - Use of Material from BSE Positive Cattle in Animal Feed doc pdf	09/30/04
176	Guidance for Industry #176 - Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances - VICH GL-39, Draft Guidance - May 24, 2005 doc pdf	05/24/05
177	Guidance for Industry #177 - Specifications: Test Procedures and Acceptance Criteria for New Biotechnological/Biological Veterinary Medicinal Products - VICH GL-40, Draft Guidance - May 24, 2005 doc pdf	05/24/05

*VICH indicates the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products; FDA, Food and Drug Administration; ADI, Acceptable Daily Intake; CGMP, current good manufacturing practice; and PAT, Process Analytical Technology.

- It will ban the use of “poultry litter” as a feed ingredient to ruminant animals since the litter, which consists of bedding, spilled feed, feathers and fecal matter may contain protein that is prohibited in ruminant feed, such as bovine meat and bone meal.
- The rule will ban the use of “plate waste” as feed ingredient for ruminants. Plate waste consists of uneaten meat and other meat scraps that are currently collected from some large restaurant operations and rendered into meat and bone meal for animal feed.
- It will require that equipment, facilities or production lines are dedicated to no ruminant animal feeds if they use protein that is prohibited in ruminant feed.

To accompany these new measures, the FDA will increase its inspections of feed mills and renderers. FDA will itself conduct 2,800 inspections and will fund 3,100 contract inspec-

tions of feed mills, renderers, and other firms that handle animal feed and feed ingredients. The FDA will also be working with Congress to consider proposals to assure that these protective measures are implemented as effectively as possible. Furthermore, the FDA is investing in the development of diagnostic tests that will rapidly detect the presence of prohibited materials in animal feed and in the development of methods for testing animal feeds and other products for contamination with the vector associated with BSE.⁵

Counterterrorism issues have also been in the forefront. One of the focal points of these concerns is the potential terrorist threats to the safety of our food supply. In this regard, the FDA is responsible for protecting against potential threats to the overall safety of food products derived from animals.

CVM is working with other federal agencies to help the country prepare for a biological emergency, natural disaster or terrorist attack by insuring the availability of a safe and adequate supply of animal drug products and a safe animal

feed supply system.⁶ In an announcement dated 2/3/04, President George W. Bush established national policy (Homeland Security Presidential Directive No. 9) to defend the agriculture and food system against terrorist attacks, major disasters, and other emergencies.⁷ This directive includes the following goals and protective measures:

- Awareness and Warning
 - Build upon and expand current monitoring and surveillance programs.
 - Develop and enhance intelligence operations and analysis capabilities focusing on the agriculture, food, and water sectors.
 - Create a new biological threat awareness capacity that will enhance detection and characterization of an attack.
- Vulnerability Assessments: expand and continue vulnerability assessments of the agriculture and food sectors.
- Mitigation Strategies
 - Prioritize, develop, and implement mitigation strategies to protect vulnerable critical nodes of production or processing from the introduction of diseases, pests, or poisonous agents.
 - Build on existing efforts to expand development of common screening and inspection procedures for agriculture and food items entering the United States (United States) and to maximize effective domestic inspection activities for food items within the United States.
- Response Planning and Recovery: included under this section of the directive is the development of:
 - A National Veterinary Stockpile (NVS) containing sufficient amounts of animal vaccine, antiviral, or therapeutic products to appropriately respond to the most damaging animal diseases affecting human health and the economy and that will be capable of deployment within 24 hours of an outbreak.
 - A National Plant Disease Recovery System (NPDRS) capable of responding to a high-consequence plant disease with pest control measures and the use of resistant seed varieties within a single growing season to sustain a reasonable level of production for economically important crops.
- Outreach and Professional Development:
 - Establish an effective information sharing and analysis mechanism for agriculture and food.
 - Develop and promote higher education programs for the protection of animal, plant, and public health.

- Provide grants to universities for interdisciplinary degree programs that combine training in food sciences, agriculture sciences, medicine, veterinary medicine, epidemiology, microbiology, chemistry, engineering, and mathematics (statistical modeling) to prepare food defense professionals.
- Establish opportunities for professional development and specialized training in agriculture and food protection, such as internships, fellowships, and other post-graduate opportunities that provide for homeland security professional workforce needs.
- Research and Development:
 - Accelerate and expand the development of current and new countermeasures against the intentional introduction or natural occurrence of catastrophic animal, plant, and zoonotic diseases.
 - Develop a plan to provide safe, secure, and state-of-the-art agriculture biocontainment laboratories that research and develop diagnostic capabilities for foreign animal and zoonotic diseases.
 - Establish university-based centers of excellence in agriculture and food security.

CVM Counterterrorism Projects include:

- Informing state veterinary offices about FDA's technical role in identifying and responding to an intentional or accidental contamination of animal feed.
- Assisting state authorities in acquiring the scientific and analytical expertise and capability to respond to an animal feed contamination incident.
- Developing a database with the Department of Energy and Iowa State University that enables "first responders" to a bioterrorism incident involving animals:
 - To recommend appropriate sampling techniques and sample handling for laboratory analysis.
- Coordinating counterterrorism activities with other Federal, State, local and foreign regulatory agencies.
- Partnering with the FDA Center for Food Safety and Applied Nutrition (CFSAN) in engineering the regulations required under the Bioterrorism Act of 2002 and for determining how best to evaluate the impact of food and animal related bioterrorism activity on human health.
- Working with United States feed industry associations to develop bio-security awareness guidelines for the feed industry.
- Intensifying the review of products offered for import and collaborating with the United States Customs Service at ports on safety and security issues.

- Establishing and maintaining the Feed Contaminant and Tissue Residue Compliance Programs, which play an important role in the early detection of chemical and biological contaminants in the animal feed supply.
- Developing analytical methods to detect the presence of toxic substances that could be introduced into United States animal feed supplies. Once developed and optimized, these methods would be used to detect toxic substances in animal feed.
- Detection of multi-drug resistant foodborne bacterial pathogens through participation in national surveillance programs including FoodNet and PulseNet.

Food safety is not the only focus for handling potential terrorist threats. For example, most of us can recall public concerns expressed in response to the potentially fatal consequences of inhalation exposure to anthrax spores. However, few people recognize that similar concerns need to be addressed for the safety of companion animals. In this issue, on behalf of The American Academy of Veterinary Pharmacology and Therapeutics and The American College of Veterinary Clinical Pharmacology, Dr. Cory Langston presents a white paper regarding the appropriate therapeutic and prophylactic interventions that need to be taken if a dog is exposed to anthrax spores.

Another potential point of concern is the safety and effectiveness of compounded drug products. Challenges associated with assuring the quality of compounded drug products affect both human and veterinary medicine. In a recent article by Tamara Nordenberg,⁸ the dilemma of juggling risks and benefits of compounding are examined. This includes the role of compounding in providing custom-made versions of drugs for situations such as when a patient is allergic to “inactive” ingredients found in marketed products and the need for alternative dosage forms in elderly and pediatric patients. When compounded products are administered to food-producing animals, there is also the need to insure that such uses do not result in violative drug residues (thereby resulting in human food safety concerns).

Within the framework of veterinary medicine, when an approved product is available, a compounded product is not permitted to be used unless the use conditions meet the criteria in the Animal Medicinal Drug Use Clarification Act (AMDUCA).⁹ The key constraints of AMDUCA are that any extralabel uses must be by or on the order of a veterinarian within the context of a veterinarian-client-patient relationship, must not result in violative residues in food-producing animals, and the use must be in conformance with the implementing regulations published at 21 CFR Part 530. On July 14, 2003, FDA published a Federal Register announcement

on the availability of a revised Compliance Policy Guide (CPG) section 608.400 entitled “Compounding of Drugs for Use in Animals.”¹⁰ The purpose of the revised CPG is to ensure that the Agency’s enforcement policy regarding the compounding of drugs intended for use in animals is consistent, to the extent practicable, with its enforcement policy regarding the compounding of drugs intended for use in humans.¹¹ This CPG replaced the 1996 CVM CPG. Although CPGs are generally intended as internal guidance, they are made public to enhance the transparency of FDA’s current thinking. Along these lines, this theme issue contains a review by Dr. Mark Papich which addresses some of the issues affecting the compounding of pharmaceuticals for veterinary use.

In the 2002 animal health theme issue of *AAPS PharmSci*, Drs. Arthur L. Craigmill and Kristy A. Cortright wrote an article on the *Evaluation of Human Food Safety for Veterinary Drugs*.¹² In that article, they described the assumptions and algorithms associated with the establishment of a withdrawal time (time between the last drug administration and the slaughter of the animal for human consumption), the latter being based upon some maximum allowable daily intake (MRL) of drug residues in food. Oftentimes, there are international differences in the allowable levels of drug residues. These differences can affect the international trade of food products derived from animals, including meats, milk and eggs. Within this second theme issue, Dr. James MacNeil provides an overview of the international harmonization efforts associated with the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). He notes that through the establishment of expert committees, agreements are established regarding the safety of food additives present as residues resulting from the use of pesticides or veterinary pharmaceuticals. The resulting decisions are pivotal to the elimination of international trade barriers associated with products intended for human consumption.

Another aspect of food safety is the safety of food additives. CFSAN is involved in determining the safety of food additives, using animal models for calculating an acceptable daily intake of these substances. In this theme issue, Dr. William Roth of CFSAN reviews methods used to assess the safety of these additives. His review provides an overview of the use of animal models as surrogates for human drug exposure, the physiological and pharmacokinetic models used for generating safety assessments, and the use of information on drug chemical properties to predict the steady-state plasma and tissue levels of a test material. Ultimately, the safety assessment of food additives are based upon the mathematical extrapolation of the highest dose associated with no adverse effect in test animals to arrive at an acceptable daily intake (ADI) for humans.

New in this theme issue is information on pharmaceutical product development for aquatic species. Aquaculture is becoming an increasingly important source of fish protein for human consumption. As the number of aquaculture facilities grows, so does the need to develop safe and effective compounds for treating fish diseases. Most scientists have little information regarding the enormous challenges facing both drug sponsors and regulators when dealing with pharmaceutical dosage forms for aquatic species. For example, unlike mammals (and other homeotherms), the physiological characteristics of fish can undergo dramatic changes as water conditions (eg, temperature and salinity) change as a function of season. Drugs that are safe at one life stage may be lethal when administered in a different life stage. In addition, gender itself can change, depending upon the conditions to which the fish is exposed. If these variables don't make the situation sufficiently complex, add the lack of funding received for developing these drugs (due to the lack of economic incentives), the fact that drugs administered to fish can have significant environmental impact (eg, entry into waterways), that fish can be exposed to and absorb dissolved drug that may have otherwise been intended for oral administration, and the rapid growth of the aquaculture industry as people increase their consumption of fish. Considering these points, Dr. Susan Storey has provided a review of the challenges and concerns associated with the regulation of drugs for use in aquatic species. In addition, Dr. Renate Reimschuessel has provided access to the CVM aquaculture database, a searchable database providing information on residues and pharmacokinetics of various compounds (drugs and pesticides) in fish. It contains information from over 275 articles and includes data from 50 species (40 genera) of fish.

It is our hope that these theme issues enhance interdisciplinary communication and encourage the formation of collaborative bridges between veterinary and human health counterparts. It is also our hope that animal health scientists unfamiliar with many of the human health issues will gain new insights by viewing other volumes of *AAPS Journal* (formerly *AAPS PharmSci*).

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