FDA VETERINARIAN

Center for Veterinary Medicine

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DR. VAUGHN SELECTED AS ONADE DIRECTOR

Dr. Steven D. Vaughn has been selected to fill the position of Director of FDA's Center for Veterinary Medicine's (CVM's) Office of New Animal Drug Evaluation (ONADE.) Dr. Vaughn assumed the role of ONADE Director on November 3, 2002.

Dr. Vaughn has held positions in both CVM's Office of Surveillance and Compliance (OS&C) and ONADE. He joined CVM in 1987 as a veterinary medical officer in OS&C's Division of Surveillance and in 1991 was promoted to Chief of the Antiparasitic and Physiological Drugs Branch in the Division of Therapeutic Drugs for Food Animals in ONADE. In 1992, Dr. Vaughn became the Director of ONADE's Division of Therapeutic Drugs for Food Animals and has served with distinction as a valued member of the ONADE management team. In recent months, Dr. Vaughn has provided invaluable expertise to the Center on such issues as user fee legislation, activity-based costing, and strategic planning.

Photo by Eric Dunbin

Dr. Steven D. Vaughn

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CVM JOINS PEW INITIATIVE FOR PUBLIC MEETING ON CLONING

by Jon F. Scheid

As the Center for Veterinary Medicine (CVM) is nearing a decision on the type of regulatory structure that will be needed for cloned animals, it has sponsored a public meeting along with the Pew Initiative on Food and Biotechnology to give all parties—including the companies developing the cloned animals, the livestock producers who might use cloned animals, and consumer groups—a chance to share their perspectives on the issue.

"New technologies like cloning bring up many questions, and not just from scientists, but from consumers, livestock producers, and food companies," according to Michael Fernandez, director of science for the Pew Initiative. "We are pleased to have a chance to work with CVM to provide a forum for all parties to talk about these important issues," he added.

The meeting, "Animal Cloning and the Production of Food Products—Perspectives from the Food Chain," held September 26 in Dallas, Texas, included time for an open microphone so any attendees could make comments for the record. (You can listen to an audio web cast recording of the conference and review some of the presentations at *http://pewagbiotech.org/events/0924/*.)

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PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

DR. VAUGHN SELECTED AS ONADE DIRECTOR (Continued)

Dr. Vaughn earned a D.V.M. degree from the University of Georgia in 1978. He has nine years of clinical practice experience. Dr. Vaughn's appointment comes at a time when the Office of New Animal Drug Evaluation is facing unprecedented challenges. Rapid advances in the field of animal biotechnology, the increasingly prominent issue of antimicrobial resistance, and the potential for user fee and minor use/minor species legislation represent just a few of the many issues facing ONADE.

Dr. Andy Beaulieu has been Acting ONADE Director, and he will now resume his position as the Associate Director for Animal Health Policy and Operations.

. . . PUBLIC MEETING ON CLONING (Continued)

SCNT Cloning Technology

While the concept of cloning is not new, it has taken on new meaning with the development of the "somatic cell nuclear transfer" technology, also know as SCNT. This was the technology used to clone Dolly the sheep in 1996, according to John Matheson, senior regulatory scientist for CVM. The SCNT type of cloning has the potential to produce a great number of all species of food-producing animals, he said at the meeting.

SCNT technology involves replacing the nucleus in an egg with the nucleus from a cell of the animal to be cloned. The resulting embryo is implanted into a surrogate mother. With this technology, a company could make hundreds, even thousands, of copies of one animal.

The livestock production industry tried cloning in the past, using embryo splitting or blastomere cloning. Both methods turned out to be expensive because only a few animals could be produced from one source animal, and unpredictable because scientists couldn't clone an animal they knew. Instead, they were cloning an embryo, which had unknown traits. With SCNT, technicians can clone the adult animal, so they will know what traits to expect.

The cloned animal itself is not likely to be used for food. It will instead be used to produce high-quality offspring that will be used for food. The results of cloning could be spread throughout the food supply, which was not the case with the earlier types of cloning.

CVM Director Dr. Stephen Sundlof told the audience that the general public still might not be focusing on the agricultural uses of SCNT. After Dolly was born, the public's initial attention was focused on the use of the technology to clone humans. Scientists, meanwhile, were interested in cloning animals for use in producing biomedical products. But the agricultural community, which had tried cloning unsuccessfully before, quickly starting working with the SCNT technology. As the agriculture community became interested, CVM began to take steps to evaluate the technology for food and animal safety issues, before cloned animals enter the food chain.

In 2003

Matheson told the audience that CVM plans to develop its policy on regulating clones sometime in 2003, possibly in the first half of the year. Before that, the Center will develop and release two "White Papers," one describing food safety risks from cloned animals and their progeny, and one describing health risks to individuals and populations of cloned animals and their offspring. The White Papers could be released by the beginning of the year, he said.

The White Papers are risk assessments. Any policy or guidance is a risk management document. The Center will use the White Papers as the basis for developing risk management or regulatory measures that are appropriate for the food and animal health risks. When the guidance or policy is announced, he said, the Center will ask for public comment.

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FDA VETERINARIAN

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. . . PUBLIC MEETING ON CLONING (Continued)

According to Matheson, "There are some basic principles that we are committed to following in arriving at a risk assessment for animal clones and their offspring."

One is transparency. The Center will use only that information that is publicly available to make its risk assessments. To the extent possible, CVM officials are planning to use published, peer-reviewed literature as the basis for developing the risk assessment, Matheson said. "You will know what we know about the risks," he added.

The second is that CVM will limit its policy decisions to those that can be made based on science. CVM will consider safety of food, and safety to the animal and to the environment. Other factors, such as the effect cloning regulations could have on trade, livestock industry economics, or social and aesthetic issues, may be legitimate to discuss, he said, but cannot be part of CVM's policies, because CVM's authority does not extend to those issues. "We're not making any judgment about a consumer's 'right to choose' or 'right to know,' only to say that those rights are determined by the Congress, not CVM," he added.

Symposium's Goal

According to Dr. Sundlof, the goal of the cloning symposium was to have all sectors of the food production and consumption in the same room to discuss their perceptions about SCNT cloning and identify any areas that need to be addressed.

CVM worked with the Pew Initiative on Food and Biotechnology whose mission is "to be an independent and objective source of credible information on agricultural biotechnology for the public, media, and policymakers." The Pew Initiative is a project of the University of Richmond and the Pew Charitable Trusts.

Along with officials from CVM, the program included representatives of companies already developing SCNT cloned animals, including Steven Stice from ProLinia, and Erik Forsberg of Infigen, Inc. The panel included scientists: Dr. Eric Hallerman who worked on the National Academy of Sciences/National Research Council team that developed a report on cloning, released in August (See *FDA Veterinarian*, September/October 2002, page 1), and Dr. Mark Westhusin of the College of Veterinary Medicine, Texas A&M University.

Buyers and sellers of cloned animals were represented by Donald Coover of SEK Genetics and Ron Gillespie of Cyagra. Food producers were represented by Christopher Galen of the National Milk Producers Federation, and Eric Hentges of the National Pork Board.

Consumers were represented by Carol Tucker Foreman of the Consumer Federation of America, and Gregory Jaffe of the Center for Science in the Public Interest.

More information about the meeting and many of the presentations are available on the Pew Initiative's web site, listed above.

Jon Scheid is the Director of CVM's Communications Staff.

VETERINARIANS MAY NOT PRESCRIBE THALIDOMIDE

In response to inquiries received by CVM concerning thalidomide, the following statements explain in detail the reasons why veterinarians are not able to prescribe thalidomide for use in their animal patients.

Thalidomide is approved as a drug for use in humans for the treatment of skin lesions associated with erythema nodosum leprosum. Because of thalidomide's potential for causing birth defects, FDA invoked unprecedented authority to tightly control the marketing of thalidomide in the United States through the *S.T.E.P.S.*™ (System for Thalidomide Education and Prescribing Safety) program. Thalidomide was the first drug approved under the provisions of § 314.520 (approval with restrictions to assure safe use). Section 314.520 states that if FDA concludes that a drug product can be safely used only if distribution or use is restricted, FDA will require such post-marketing restrictions as are needed to assure safe use of the product. The restricted distribution program for thalidomide is specifically designed to ensure that no human fetus is exposed to the drug.

Due to the complexities of the *S.T.E.P.S.*™ program, which was specifically designed for human patients,

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VETERINARIANS MAY NOT PRESCRIBE THALIDOMIDE . . . (Cont.)

Veterinarians may not prescribe thalidomide for use in their animal patients.

and the need for careful assessment of all adverse reactions and possible fetal exposure, the manufacturer of the approved product will not knowingly register veterinarians as prescribers. Therefore, veterinarians are unable to prescribe the approved human drug.

FDA recognizes the need for veterinarians to have access to a variety of drug products that are not specifically approved for use in animals and provides several avenues for allowing such use under most circumstances.

Extra-label use of approved human drugs in non-food producing animals is generally permitted under § 530.30(a), except when the public health is threatened. FDA has found that thalidomide poses a threat to public health unless access to the drug and its use are restricted. Thus, it is not available to veterinarians under this regulation because veterinarians cannot register as prescribers under the mandatory restricted distribution program.

FDA has found that thalidomide poses a threat to public health unless access to the drug and its use are restricted.

FDA may exercise enforcement discretion on a case-by-case basis to allow veterinarians to use unapproved drugs not otherwise provided for by regulation for investigational purposes on an experimental basis in the United States. FDA will not exercise its enforcement discretion for veterinary use of thalidomide because any distribution of thalidomide outside of the *S.T.E.P.S.*™ program, without the safeguards and monitoring provided by the program, would defeat the Agency's efforts to restrict access to the drug and ensure a zero tolerance for thalidomide exposure of a fetus during human pregnancy. Thalidomide use in such uncontrolled channels could result in human fetal exposure via diversion or accidental exposure.

FDA may also exercise regulatory discretion to permit the importation of unapproved products into the United States for personal use. Before FDA will permit personal importation, it will consider whether importation of the product will represent an unreasonable risk. Due to the serious health risks associated with use of thalidomide in inadequately controlled settings, it is considered inappropriate for release under the personal importation guidance and all imports of thalidomide, whether intended for human or animal use, will be detained. ■

REMINDER – EXTRA-LABEL USE OF FLUOROQUINOLONES PROHIBITED

FDA's Center for Veterinary Medicine (CVM) reminds veterinarians that extra-label use of fluoroquinolone antibiotics in food-producing animals is prohibited. CVM has received some information indicating that fluoroquinolone antibiotics such as enrofloxacin are being prescribed for use in food-producing animals including lactating dairy cattle for which they are not approved.

The prohibition against extra-label use of fluoroquinolones is based on a finding by CVM that the extra-label use of these antibiotics in food-producing animals presents a risk to the public health for the purposes of the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994. These extra-label uses are capable of increasing the antibiotic resistance of the bacteria that can cause human illness and that are present in treated animals at the time of slaughter. Information about this prohibition was published in the May 22, 1997, *Federal Register*.

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REMINDER – EXTRA-LABEL USE OF FLUOROQUINOLONES PROHIBITED (Continued)

AMDUCA amended the Federal Food, Drug, and Cosmetic Act to allow licensed veterinarians to prescribe extra-label uses of approved animal drugs and human drugs in animals. Section 2(a)(4)(D) of the AMDUCA provides that the Agency may prohibit an extra-label drug use in animals if, after affording an opportunity for public comment, the Agency finds that such use presents a risk to the public health.


Photo by Karen Kandra

The following drugs (both animal and human), families of drugs, and substances are prohibited for extra-label uses in all food-producing animals:

- Chloramphenicol;
- Clenbuterol;
- Diethylstilbestrol (DES);
- Dimetridazole;
- Ipronidazole;
- Other nitroimidazoles;
- Furazolidone, Nitrofurazone, other nitrofurans;
- Sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine);
- Fluoroquinolones; and
- Glycopeptides.

Veterinarians who have questions about AMDUCA or the extra-label use of drugs may contact FDA/CVM Division of Compliance, 7500 Standish Place, HFV-230, Rockville, MD 20855, 301-827-1168.

FDA LEVERAGING INITIATIVE IN LINE WITH PRESIDENT'S MANAGEMENT AGENDA: PART II - LEVERAGING ACTIVITIES IN CVM

by David Batson, Ph.D. and Melissa Starinsky

Introduction

This is the second in a series of articles on leveraging in the Food and Drug Administration (FDA), in which we will discuss and give examples of specific leveraging projects in the Center for Veterinary Medicine (CVM). The first article, which appeared in the July/August 2002 edition, gave a brief overview of leveraging and why leveraging is important to CVM. This article will describe three specific CVM leveraging projects that involve a Cooperative Agreement, an Interagency Agreement, and a Cooperative Research and Development Agreement (CRADA), and how they impact the mission of the Center.

Cooperative Agreements

A cooperative agreement involves collaboration between two or more parties in which all of the parties contribute programmatic and/or funding resources. CVM has a long history with cooperative agreements and views these collaborations as mutually beneficial for all parties, with the ultimate beneficiary being the public health.

An example of a cooperative agreement in which CVM is currently involved is a project with the Fundacion Mexicana para la salud, International Hospital O'Horan, Yucatan, Mexico. Under this agreement, CVM is providing funding and scientific expertise and the Fundacion is providing scientific expertise, facilities, samples and equipment to work on the issue of antimicrobial resistance. It is anticipated that this project will contribute to the development of an international database that will utilize standardized microbial susceptibility testing methods and allow for an

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FDA LEVERAGING INITIATIVE . . . (Continued)

international monitoring system to flag the emergence of resistant microbial strains. The system will permit the examination of microbial susceptibility patterns across participating nations. Such a multinational surveillance program results in improved detection of epidemics and for earlier responses to the emergence of resistant pathogens. On an international scale, this provides greater public health protection against multidrug resistant pathogens such as *Salmonella enterica* Typhimurium DT 104.

Interagency Agreements

Interagency agreements provide a mechanism for sharing of knowledge, personnel, or other resources to strengthen programs of mutual concern between two or more Federal agencies. The interagency agreement is also a mechanism for eliminating overlap or duplication of effort.

An example of an interagency agreement that is currently under way in CVM is a project between the U.S. Geological Survey (USGS) and the FDA. Under this agreement, the USGS is providing funding and scientific expertise while the FDA is contributing scientific expertise, facilities and equipment. The information generated will benefit the FDA in providing the required regulatory method for the confirmation of p-toluenesulfonamide (p-TSA) in fish. p-TSA is a metabolite and marker residue of chloramine-T which may be used in fish raised in public aquaculture. This method will be available to the laboratories of FDA's Office of Regulatory Affairs, to monitor the food supply for residues of p-TSA, and also to support a New Animal Drug Application for the use of chloramine-T to treat bacterial gill disease. Since so few drugs are approved for use in aquatic species, this method will benefit the FDA mission of promoting the availability of a safe and nutritious food supply.

Cooperative Research and Development Agreements (CRADAs)

CRADAs involve collaborative efforts between CVM and one or more partners (academia, industry, not-for-profit or, for-profit companies, and State and local governments). The CRADA is intended to help develop technology, inventions, training programs, etc., that will facilitate achievement of mission-related goals. The CRADA partner receives some benefit from the collaboration and may provide funds to be used on the project. A recent CVM CRADA with the Freshwater Institute of Shepherdstown, West Virginia, resulted in the gathering of information about the development of antimicrobial drug resistance in recirculating aquaculture systems. In this CRADA, CVM provided scientific expertise, equipment, supplies and facilities; the Freshwater Institute provided funding, study samples and scientific expertise in support of the effort. The proliferation of resistant microbial strains that can affect aquatic species is a national concern that is currently being addressed by the Center's Food Safety Program. This project also may provide useful information to the aquaculture industry by providing information regarding the safety of recirculating water systems.

In the next article in this series, two executed CRADAs will be discussed in detail. Subsequent articles will provide similar levels of detail on other types of agreements. We hope these discussions will stimulate interest in the development of new opportunities for enhancing FDA's scientific base through the use of leveraging.

If you have any questions on leveraging or if you have an interest in initiating a collaboration with FDA's Center for Veterinary Medicine please contact David Batson at (301) 827-8021 or Melissa Starinsky at (301) 827-5309.

Dr. Batson is a Health Scientist Administrator with CVM's Office of Research, and Ms. Starinsky is a Management and Program Analyst with CVM's Office of Management.

CVM ATTENDS WORLD DAIRY EXPO AND AVMA CONVENTION

CVM'ers Deborah Brooks, Joanne Kla, and Karen Kandra staffed a booth at the 36th World Dairy Expo, held recently in Madison, WI. Located at the Alliant Energy Center, the Expo attracted 70,100 people from the dairy industry from 81 countries. That is an increase from the last year's event when 62,075 attendees from 66 countries attended the world's largest strictly dairy focused trade show. Canada, Japan, Mexico, Germany and Netherlands/Holland provided the most foreign attendees.

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. . . WORLD DAIRY EXPO AND AVMA CONVENTION (Continued)

Charles D. Price, Senior Regional Milk Specialist from FDA's Chicago office, assisted CVM'ers in responding to questions from visitors to the booth. CVM handouts included *The Judicious Use of Antimicrobials for Dairy Producers* and *The Judicious Use of Antimicrobials for Dairy Veterinarians*, as well as the new Spanish versions of the *Small Entity Compliance Guides for Renderers; Protein Blenders, Feed Manufacturers, and Distributors; Producers with On-Farm Mixing Operations; and, Producers Without On-Farm Mixing Operations.*

More than 8,000 veterinarians and others attended the 2002 American Veterinary Medical Association's (AVMA) Convention at the Gaylord Opryland Resort and Convention Center in Nashville, TN last July.

CVM Director, Dr. Stephen F. Sundlof, presented a speech giving an overview of CVM's food safety activities, including antimicrobial resistance, illegal drug compounding, biotechnology, and dioxins.

Dr. David G. White of CVM's Office of Research presented current CVM research and regulatory activities associated with antimicrobial resistance, including research detailing the prevalence of antimicrobial resistant zoonotic foodborne bacterial pathogens in domestic and imported retail foods and animal feeds.

The Center for Veterinary Medicine staffed a booth in commercial space that attracted hundreds of veterinarians, veterinary technicians, students, and guests. Jon Scheid and Karen Kandra from CVM's Communications Staff, and Dr. Doug Oeller from the Division of Therapeutic Drugs for Non-Food Animals responded to questions, and distributed publications such as *FDA and the Veterinarian*, the Judicious Use Guides, and the *FDA Veterinarian*, along with stickers, magnets, and stuffed animals to a few lucky youngsters. This was a wonderful opportunity to converse with stakeholders, and pass along valuable information.

Jon Scheid and Karen Kandra assist a visitor during the AVMA Convention in Nashville.

DEVELOPMENT OF A STANDARDIZATION SUSCEPTIBILITY TESTING METHOD FOR *CAMPYLOBACTER*

by P. F. McDermott, Ph.D., S. M. Bodeis and R. D. Walker, D.V.M.

Campylobacter is a leading cause of human bacterial gastroenteritis worldwide. It is estimated that there are more than 2,000,000 cases estimated each year in the U.S. *C. jejuni* and *C. coli* are the most commonly isolated *campylobacter* species in cases of human disease. Other important species associated with disease in humans include *C. lari*, *C. jejuni* subspecies *doylei* and *C. fetus*. *Campylobacter* is considered mainly a foodborne pathogen. Contaminated milk, water, chicken, pork, beef, lamb, pets, and seafood are all known to contribute to human infections. In the U.S., the majority of sporadic cases of *Campylobacter* infection have been linked to mishandled or undercooked poultry meats. Surveillance data show that approximately 70-80% of retail raw chicken meats are contaminated with *Campylobacter.*

Intestinal campylobacteriosis is usually a mild to moderate self-limiting diarrheal disease, accompanied by fever and abdominal cramping. As for most cases of acute diarrhea, treatment is usually supportive, consisting of rehydration and symtomatic therapy. Antimicrobial therapy is employed in relapsing or severe intestinal infections or when extra-intestinal infections occur, such as bacterimia, endocarditis, or meningitis. The latter conditions arise mostly in elderly and immunocompromised patients. When antibiotics are recommended, macrolides (*e.g.*, erythromycin) and

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. . . TESTING METHOD FOR *CAMPYLOBACTER* (Continued)

fluoroquinolones (*e.g.*, ciprofloxacin) are the drugs of choice. Doxycycline and gentamicin are sometimes used as alternative drugs for treatment. For infections caused by *C. fetus*, meropenem is one of the treatments of choice. Decreased susceptibility of *campylobacter*, particularly to the fluoroquinolones, has made empiric therapy less reliable. Effective patient management is further complicated by the lack of a standardized *in vitro* susceptibility testing method and interpretive criteria, which makes choosing an appropriate anti-infective agent difficult. A standardized *in vitro* antimicrobial susceptibility testing method, including the appropriate quality control organisms, is essential for generating accurate and reproducible susceptibility testing results.

In the United States, the National Committee for Clinical Laboratory Standards (NCCLS) is the recognized organization for developing standards for *in vitro* susceptibility testing of bacterial pathogens. To develop a reliable testing procedure for *Campylobacter*, a multiple-laboratory trial was conducted in accordance with NCCLS guidelines. Preliminary studies had established a suitable growth medium (Mueller-Hinton agar with 5% sheep blood), atmospheric conditions (85% N, 15% CO_2, 5% O_2), incubation temperature (36°C, 48 hr) and identified *C. jejuni* ATCC 33560 as the quality control (QC) strain. In subsequent deliberations, the NCCLS requested a study to compare testing at both 36°C for 48 hours and 42°C for 24 hours. In this study, they requested that five antimicrobial agents commonly used to treat human campylobacteriosis (ciprofloxacin, doxycycline, gentamicin, erythromycin, and meropenem) be tested. The multi-laboratory trial also included testing a collection of human isolates of *Campylobacter*, in order to validate the method with clinical strains.

The participating laboratories were: Clinical Microbiology Institute, Wilsonville, OR; Focus Technologies, Herndon, VA; Duke University Medical Center, Durham, NC; Michigan State University, College of Medicine, East Lansing, MI; The Food and Drug Administration, Center for Veterinary Medicine, Office of Research, Laurel, MD; Danish Veterinary Institute, Copenhagen, Denmark; Division of Immunity and Infection, The Medical School, University of Birmingham, Birmingham, UK; Department of Microbiology and Public Health, University of Alberta Hospital, Edmonton, Alberta, Canada; and Abbott Laboratories, Abbott Park, IL. These laboratories were chosen for their expertise in susceptibility testing of *Campylobacter.*

In each laboratory, 10 replicates of *C. jejuni* ATCC 33560 and 21 human isolates of *Campylobacter* were tested daily for two days using agar dilution. The 21 clinical isolates consisted of five *C. jejuni*, five *C. coli*, five *C. doylei*, three *C. fetus* and three *C. lari.* Each isolate was tested against the five antimicrobial agents at both 36°C for 48 hr and 42°C for 24 hr. Testing involved 10 independent suspensions of the QC organisms, *C. jejuni* ATCC 33560, and each of the 21 human clinical isolates per day for two days. This resulted in a total of 11,340 data points for the human clinical isolates (21 isolates x 5 drugs x 3 medium lots x 2 days x 2 temperatures x 9 laboratories).

The minimal inhibitory concentration (MIC) results for the QC organism against the five antimicrobial agents were highly reproducible within and between laboratories and with both incubation conditions. For all drugs, the QC limits encompassed more than 95% of the observed values under both incubation conditions. The MIC results for the 21 human clinical isolates showed that they spanned an MIC range around the established QC ranges. Comparison of the two testing procedures showed that *C. jejuni* and *C. coli* could be reliably tested using either incubation temperature. In contrast, there were many instances where *C. lari*, *C. jejuni* subspecies *doylei*, and *C. fetus* isolates failed to grow at 42°C. Given these variations in growth among different isolates of these species, it is recommended that these three *Campylobacter* species be tested only at 36°C.

Several *in vitro* methods have been used to measure the susceptibility of *Campylobacter* to various antimicrobial agents. Disk diffusion is attractive due to its convenience and low cost. Some researchers report consistent results obtained by disk diffusion within a single laboratory. In preliminary multi-laboratory experiments not reported here, we were unable to advance disk diffusion as a standardized method, due to very poor intra- and inter-laboratory reproducibility.

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. . . TESTING METHOD FOR *CAMPYLOBACTER* (Continued)

This problem was ascribed to the peculiar growth characteristic of *Campylobacter.* This resulted in widely different interpretations of zone sizes for the same strain/antimicrobial combinations, depending on the angle and intensity of the light source. Thus, disk diffusion should not be used for susceptibility testing organisms in this genus until growth conditions are identified that eliminate ambiguities in end point determinations.

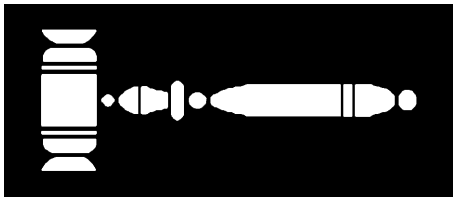
The epsilometer testing method (Etest, Solna, Sweden) is widely used to measure the antimicrobial susceptibility of *Campylobacter*. This method involves a carrier strip coated with an antimicrobial gradient that is placed on a seeded agar plate. This technique is convenient, and has the advantage of providing an MIC value. In separate studies, we have compared the Etest with the NCCLS agar dilution method at 36°C and found that, in general, the Etest endpoints fall one or more dilutions below those observed using agar dilution. Deviations from the agar dilution results were greater for certain antimicrobial agents. The availability of the agar dilution test as a standardized method will provide a reference method that can be used to advance other susceptibility testing methods that may be amenable to routine laboratory use. For example, we are currently using the method reported here to develop a standardized testing method based on broth microdilution.

The QC ranges, testing conditions and testing method, as well as the QC organism, has been accepted by the NCCLS for the susceptibility testing of *Campylobacter,* and will be published in the the M31-A2 and M7-A6 documents in 2002. In addition to improving the management of patients being treated for infections caused by *Campylobacter,* a standardized method allows for comparison of data between laboratories. This improves monitoring of susceptibility trends over time, and for precise data in both clinical studies and diagnostic laboratories.

Dr. McDermott, Ms. Bodeis, and Dr. Walker are scientists in CVM's Division of Animal and Food Microbiology, located at the Office of Research, Laurel, Maryland.

REGULATORY ACTIVITIES

by Karen A. Kandra



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

- Brian A. Sipley, Owner, BCS Farms, Peru, NY
- Andy J. Laming, Owner, Pine View Dairy, Arlington, WA
- Richard R. Talcott, Co-Owner, Ashland Farms LLC, Aurora, NY
- Charles L. Guard, DVM, Cornell University, Ithaca, NY
- Gary A. Gorzeman, Owner, Gorzeman Dairy Idaho, Gooding, ID
- John Reitsma, Co-Owner, J & J Dairy, Jerome, ID

The above violations involved illegal residues of sulfadimethoxine in a cow, neomycin in a calf, penicillin in a cow, sulfamethoxazole in a veal calf, penicillin in a downer cow, and penicillin in a dairy cow.

A warning letter was issued to Thomas A. Kruse, President, Iowa Veterinary Supply Company, Iowa Falls, IA, for sales of prescription drugs for veterinary use that are adulterated within the meaning of Section 501(a)(5) of the Federal Food, Drug, and Cosmetic Act and misbranded within the meaning of Section 502(t)(1) of the Act. The drugs "Amoxicillin Oral Suspension USP" and "Sulfamethoxazole and Trimethoprim Oral Suspension USP" among others, are human drugs that are being dispensed for animal use without the required labeling, including adequate directions for use.

INTERNATIONAL ACTIVITIES

VICH 2

Approximately 200 participants attended the Second Conference of the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Products (VICH 2) held in Tokyo, Japan on October 10-11, 2002. Seven CVM experts attended this meeting and the six Working Group and Steering Committee meetings held before and after VICH 2.

VICH is an international cooperation program of industry and government participants from Japan, the European Union, and the United States. The goal of VICH is to develop international guidelines for the registration of veterinary medicinal products.

In the photo, keynote speakers prepare for their presentations at the opening VICH plenary session (from left to right are: Dr. Merton V. Smith, Special Assistant for International Activities, Center for Veterinary Medicine, FDA; Dr. James E. Pearson, Head of the Scientific and Technical Department of the Office International des Epizooties (OIE); and Dr. Shunichi Ijichi, Director of the Animal Health Division in the Japanese Ministry of Agriculture, Forestry, and Fisheries (MAFF).

U.K. Scientist Visits OR

Photo by Karen Kandra

Dr. Michael Roberts, CEO of the Central Science Laboratory in York, England visited CVM's Office of Research (OR) in Laurel, Maryland on November 7. The Central Science Laboratory is involved with methods for drug residues and microbiological tests for food. They have developed a rapid method for chloramphenicol in honey and in chicken. They are looking for opportunities to collaborate with the Center.

Dr. Linda Youngman, Acting Director of OR, Dr. Merton Smith, CVM's Special Assistant for International Activities, Dr. Michael Roberts, and Dr. Stephen F. Sundlof, Director of CVM are shown in the photo.

CVM STUDENT INTERN SUMMER PROGRAM

The FDA's Center for Veterinary Medicine provides training opportunities for undergraduate, graduate and professional students. These training opportunites seek to promote personal development and professional skills reflective of the students' field of study. The ultimate goal is to stimulate an interest in pursuing careers significant to the Center.

Program Goals and Objectives

The "Windows to Research and Regulatory Science Student Intern Program" allows the student an educational opportunity, expands career options, and nurtures professionalism and individualized development. The CVM Research/Review Scientist benefits from hosting an intern by completion of a special research project and promoting consideration of future employment at CVM.

Student Intern Research Plan and Evaluation Plan

Each participating CVM Research/Review Scientist is asked to provide a Student Intern Project that includes a plan that states the objectives and a critical evaluation plan to be conducted at four-week intervals. It is recommended that the CVM Research/Review Scientist or a designee meet with the student on a weekly basis to best provide the mid-term and final evaluations.

Program Collaboration

This program is conducted in collaboration with the National Institutes of Health, Minority Access to Research Careers (MARC) Program, the National Science Foundation, and Alliances for Minority Participation (AMP). The Program is administrated by the CVM Equal Employment Opportunity Office, Bessie Cook, EEO Manager and Dr. Woodrow Knight, Scientific Advisor.

Applying to the CVM Student Intern Summer Program

If you are interested in doing research at CVM, you may download a copy of the application at *<http://www.fda.gov/cvm/intern/student_intern02.html>*. **The deadline for applications is February 1, 2003.** For further information or help with downloading the application, contact:

Treava S. Hopkins
WorkForce Development Specialist
Food and Drug Administration
Center for Veterinary Medicine
7519 Standish Place, HFV-1
Rockville, MD 20855

OFFICE: 301-827-4275
FAX: 301-827-4334
E-MAIL: *thopkins@cvm.fda.gov*

CVM COMINGS AND GOINGS

In an effort to keep our readers apprised of new personnel developments, we will now report new hires, retirements, and resignations of CVM personnel.

September/October Hires

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Dr. Bernadette Abela-Ridder/Microbiologist
- Dr. Julie Conwell/Staff Fellow
- Dr. Richard Ellis/Chemist
- Dr. Steven Fleischer/Veterinary Medical Officer
- Dr. Charles Gray/Staff Fellow
- Mark Jackson/Biologist
- Dr. Jun Liang/Staff Fellow
- Dr. Tammy Massie/Mathematical Statistician
- Dr. Sanja Modric/Staff Fellow
- Dr. Tomislav Modric/Staff Fellow

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Shannon Jordre/Consumer Safety Officer
- Dr. Robin Keyser/Animal Scientist

OFFICE OF RESEARCH

- Althea Glen/Microbiologist

OFFICE OF THE CENTER DIRECTOR

- Tracey Forfa/Executive Secretariat

Departures

- Dr. Allen Rudman (moved to Center for Drug Evaluation and Research)

UPDATED INFORMATION ON RUMINANT FEED REGULATIONS

FDA has issued an Advance Notice of Proposed Rulemaking (ANPRM) asking for information and views on some potential changes to its current regulation prohibiting the use of certain proteins in ruminant animal feed. The current regulation is posted on the FDA/CVM Home Page at: *http://www.fda.gov/cvm/index/bse/6597bse.htm*.

FDA put this regulation in place in 1997 to prevent the spread through animal feed of the agent of bovine spongiform encephalopathy (BSE) were it to enter the U.S. FDA is considering revising this regulation and therefore is asking the public for comment on possible modifications to the rule. This information may be used to help draft a proposed rule in the near future.

On October 30, 2001, FDA held a public hearing in Kansas City, MO to hear views from the public on the adequacy of the present BSE feed regulation. Shortly after the public hearing, the U.S. Department of Agriculture (USDA) released a report prepared by the Harvard Center for Risk Analysis (*http://www.aphis.usda.gov/oa/bse/*) on the findings of a major 3-year initiative to develop a risk assessment model that allows evaluation of the impact of various risks and potential pathways for exposure of U.S. cattle and U.S. citizens to the BSE agent. The assessment of the present situation in the U.S. using this model concluded that, due to control measures already in place, the risk to U.S. cattle and to U.S. consumers from BSE is very low. The model also demonstrated that certain new control measures could reduce the small risk even further.

USDA's BSE surveillance program supports the findings of the Harvard study that measures implemented by the U.S. government, such as early import restrictions and the feed ban have been effective in preventing the entrance and establishment of BSE in the U.S. cattle population. The USDA surveillance program, which has been in place since May 1990 and is targeted at the highest risk cattle population, has found no cases of BSE to date. Although BSE has not been detected in the U.S., the U.S. government's response to BSE has always been proactive and preventive. Therefore, USDA and FDA are interested in exploring measures that could further reduce the already small risk that BSE will enter and become established in the U.S. To that end, FDA is once again asking for information from the affected industries and the public on several ways that the animal feed regulation could be strengthened.

FDA is seeking comments regarding potential changes to its regulation prohibiting use of certain proteins in ruminant animal feed.

The USDA surveillance program, which has been in place since May 1990 and is targeted at the highest risk cattle population, has found no cases of BSE to date.

In the ANPRM, FDA solicited information and comments from those with interest and expertise in any of these five aspects of the BSE feed regulation:

1. **Excluding Brain and Spinal Cord from Rendered Animal Products**

   FDA is asking for comments on the following questions:

   - Should high risk materials such as brain and spinal cord from ruminants two years of age and older be excluded from all rendered products?
   - How feasible would it be for the rendering industry to implement such an exclusion?
   - What will be the adverse and positive impacts (economic, environmental, health, etc.) resulting from a brain and spinal cord exclusion?

2. **Use of Poultry Litter in Cattle Feed**

   FDA is seeking information on the following questions:

   - How extensive is the use of poultry litter in cattle feed in the United States?
   - What is the level of feed spillage in poultry litter?

(Continued, next page)

. . . RUMINANT FEED REGULATIONS (Continued)

- What are the methods used to process poultry litter prior to inclusion in animal feed?
- What will be the adverse and positive impacts (economic, environmental, health, etc) resulting from banning poultry litter in ruminant feed?

3. **Use of Pet Food in Ruminant Feed**

In order to assure that salvaged pet food is not used in ruminant feed despite the requirement that it be labeled with the caution statement, FDA is asking for comments on the following questions.

- Should pet food for retail sale be labeled with the statement "Do not feed to cattle or other ruminants"?
- What would be the adverse and positive impacts (economic, environmental, health, etc.) of such a labeling requirement?

4. **Preventing Cross-Contamination**

The Agency is asking for comments on the following questions:

- Are there practical ways, other than dedicated facilities, for firms to demonstrate that the level of "carry-over" could not transmit BSE to cattle or other ruminants? If so, what is the safe level of "carry-over" in a feed mill; and
- What is the scientific rationale used to establish this safe level?
- What steps are firms currently taking to prevent cross-contamination of prohibited protein into ruminant feed, and what are the costs of those steps?

5. **Elimination of the "Plate Waste" Exemption**

The current regulation contains an exemption that permits "inspected meat products which have been cooked and offered for human food and further heat processed for feed (such as plate waste and used cellulosic food casings)" to be fed to ruminants. FDA wishes to reconsider this exemption and is seeking information on the following questions.

- To what extent is plate waste used in ruminant feed?
- What is the composition of plate waste and what are its sources?
- How is plate waste processed prior to inclusion in ruminant feed?
- What would be the adverse and positive impacts (economic, environmental, health, etc.) from excluding plate waste from ruminant feed?

Written or electronic comments in the ANPRM should be submitted by February 6, 2003, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Electronic comments should be submitted to *http://www.fda.gov/dockets/ecomments*. All comments should include Docket No. 02N-0273.

Further information about the ANPRM may be found in the November 6, 2002, *Federal Register* (*http://www.fda.gov/OHRMS/DOCKETS/98fr/110602c.htm*) and from Ms. Linda Huntington, Executive Secretariat, Office of the Commissioner (HF-40), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-4443.

It is important to note that while FDA is seeking information on these five areas in the ANPRM, these are not the only part of the BSE feed regulation that might be changed. All parts of the current regulation are under review from both the scientific perspective and FDA's ability to enforce the regulation. ■

ANIMAL FEED USE OF MATERIAL FROM CERTAIN FREE RANGE DEER AND ELK

In response to many inquiries received as a result of a recent call to State officials, FDA has clarified its current position regarding the use in animal feed of material from free range deer and elk from areas declared by State officials to be endemic for Chronic Wasting Disease (CWD) and/or to be CWD eradication zones.

(1) Material from CWD-positive animals may not be used in any animal feed or feed ingredients. Animal feed and feed ingredients containing material from a CWD-positive animal would be considered adulterated. We believe that any such adulterated feed or feed ingredients should be recalled or otherwise removed from the marketplace.

(Continued, next page)

ANIMAL FEED USE . . . (Continued)

(2) FDA strongly advises that materials from untested or CWD-test-negative free ranging deer and elk in areas declared by States to be endemic for CWD or a CWD eradication zone no longer be entered into the animal feed system. Under present circumstances, FDA does not believe that feed previously made from such materials needs to be recalled.

(3) FDA continues to consider materials from free range deer and elk in areas not declared by States to be endemic for CWD or a CWD eradication zone (NON-ENDEMIC areas) to be acceptable for use in non-ruminant animal feeds in accordance with current Agency regulations Title 21, Part 589.2000 of the *Code of Federal Regulations* http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr589_01.html>. Under present circumstances, FDA does not believe that non-ruminant feed made from free range deer and elk in NON-ENDEMIC areas would need to be recalled if a State later declares the area from which the deer or elk came to be endemic for CWD or a CWD eradication zone. ■

DRAFT GUIDANCE ON ADMINISTRATIVE NADA PROCESS AVAILABLE FOR COMMENT

FDA's Center for Veterinary Medicine (CVM) announced the availability of draft guidance for industry (GFI) entitled "The Administrative New Animal Drug Application Process"(GL #132) in the November 6, 2002, *Federal Register* (*http://www.fda.gov/OHRMS/DOCKETS/98fr/110602g.htm.*)

Draft guidance #132 describes CVM's Administrative New Animal Drug Application (Administrative NADA) process. An Administrative NADA is a new animal drug application that is submitted after all of the technical sections that fulfill the requirements for the approval of the new animal drug have been reviewed by CVM, and the Center has issued a technical section complete letter for each of those technical sections.

Phased review and direct review create greater efficiencies that facilitate the approval of new animal drugs.

CVM encourages drug sponsors to submit data for review at the most appropriate and productive times in the drug development process rather than submitting all data at one time. Sponsors may submit data in support of discrete technical sections for CVM "phased review" during the investigation of the new animal drug. Phased review and direct review create greater efficiencies that facilitate the approval of new animal drugs. This draft guidance defines what an Administrative NADA is, describes the phased review process, and discusses how sponsors should submit an Administrative NADA and the time frame for review.

This draft guidance represents the CVM's current thinking on this matter. It does not create or confer any rights for or on any person and does not bind CVM or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

Draft guidance #132 is posted on the FDA/Center for Veterinary Medicine Home Page at: *http://www.fda.gov/cvm/guidance/published.htm#documents*. Single copies of the draft guidance may be obtained by writing to the Communications Staff, FDA/Center for Veterinary Medicine, 7519 Standish Place, HFV-12, Rockville, MD 20855. Please send a self-addressed adhesive label to assist in processing your request.

Comments and suggestions regarding this draft guidance should be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Submit electronic comments to *http://www.fda.gov/dockets/ecomments*. All comments should be identified with Docket Number 02D-0449, and written or electronic comments on the draft guidance should be submitted by January 21, 2003 to ensure their adequate consideration in preparation of the final document. General comments on Agency guidance documents are welcome at any time.

For questions regarding this draft guidance document, contact Gail Schmerfeld, Center for Veterinary Medicine (HFV- 100), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-1796 (e-mail: *gschmer1@cvm.fda.gov*). ■

SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Pharmacia and Upjohn Co. (NADA 135-940) (NADA 120-161)	Clindamycin Hydrochloride (Antirobe Aquadrops Liquid RX, Antirobe Capsules RX)	Dogs and Cats. For the treatment of bacterial skin infections and bacterial soft tissue infections.	**ORAL**—The supplement to NADA 135-940 for an oral liquid provides for an expanded dose range for the use of clindamycin hydrochloride in both dogs and cats for the treatment of certain bacterial infections. The supplement to NADA 120-161 for oral capsules provides for an expanded dose range in dogs and cats and for use of a 300 mg strength capsule. Infections treatable are caused by susceptible strains of coagulase-positive staphylococci such as *S. aureus*. *Federal Register* 08/27/02
Fort Dodge Animal Health Div. of American Home Products Corp. (NADA 141-189)	Moxidectin, ProHeart® 6 Sustained Release Injectable RX	Dogs. For the treatment of existing hookworm infections.	**SUBCUTANEOUS or INTRAMUSCULAR**—The supplement provides for veterinary prescription use of a sustained-release injectable moxidectin formulation for treatment of existing larval and adult hookworm (*U. stenocephala*) infections. *Federal Register* 09/13/02
Pfizer, Inc. (NADA 141-053)	Carprofen (Rimadyl®) RX	Dogs. For control of postoperative pain associated with soft tissue and orthopedic surgery.	**ORAL**—The supplement provides for the veterinary prescription use of carprofen oral caplets in dogs. *Federal Register* 10/23/02
Pfizer, Inc. (NADA 141-111)	Carprofen (Rimadyl®) RX	Dogs. For the control of postoperative pain associated with soft tissue and orthopedic surgery.	**ORAL**—The supplement provides for the veterinary prescription use of carprofen in dogs, by oral chewable tablet. *Federal Register* 10/28/02

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