FDA VETERINARIAN

Center for Veterinary Medicine

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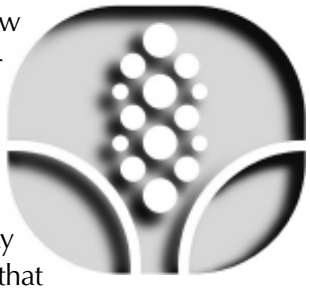
CVM TO COSPONSOR PUBLIC SYMPOSIUM ON LIVESTOCK CLONING

FDA's Center for Veterinary Medicine (CVM) and the Pew Initiative on Food and Biotechnology are cosponsoring a symposium entitled "Animal Cloning and the Production of Food Products—Perspectives from the Food Chain." The symposium, to be held on September 26, 2002, will follow a two-day symposium being held by the Pew Initiative on Food and Biotechnology entitled "Biotech in the Barnyard: Implications of Genetically Engineered Animals." Both symposia will be held at the Adolphus Hotel, 1321 Commerce Street, Dallas, Texas.

The goal of the animal cloning symposium is to provide a forum for an exchange of perspectives among the various stakeholders in animal cloning, including both brief presentations and moderated question and answer sessions. Perspectives will be shared from companies that make and sell clones, animal producers, processors, retailers, and consumers of foods derived from clones. Only cloning intended to copy animals that are not genetically engineered will be considered at the symposium, as genetic engineering in animals is the subject of the preceding two-day meeting.

In evaluating animal cloning, CVM's first, but not only, priority is to examine the safety of food products (e.g., meat, milk, eggs) from animals developed through somatic cell cloning but are otherwise unmodified.

The Pew Initiative on Food and Biotechnology (*http://pewagbiotech.org/about/*) was established to promote greater understanding of the debate on genetically modified food and other products of agricultural biotechnology, and to support development of a regulatory system for the products that protects the public health and environment and enjoys consumer confidence. The mission of the Pew Initiative is to serve as an objective, credible source of information, focusing on engaging policy makers, the media, and the public.



CVM is considering the safety of animals and their progeny that are produced as a result of somatic cell nuclear transfer (also known as somatic cell clones or NT clones.) In evaluating animal cloning, CVM's first, but not only, priority is to examine the safety of food products (e.g., meat, milk, eggs) from animals developed through somatic cell cloning but are otherwise unmodified. CVM is determining how these animals should be regulated, including whether there may be circumstances in which CVM ordinarily would not need to exert its authority.

Registration for both meetings is free. Advance registration for the symposium is required, however, as space will be limited. There will be no onsite registration permitted. Information about registering for the symposium and hotel accommodations may be found on the Pew Initiative Home Page at: *http://pewagbiotech.org/events/0924/form.php*.

Questions about participation in the animal cloning symposium may be directed to Kara Flynn, Pew Initiative on Food and Biotechnology, E-mail: *kflynn@pewagbiotech.org*, Phone: (202) 347-9044, ext. 231. ■

IN THIS ISSUE

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

FDA INCREASES SAMPLING OF IMPORTED SHRIMP AND CRAYFISH (CRAWFISH)

The Food and Drug Administration (FDA) recently announced that it will be increasing the sampling of imported shrimp and crayfish (also known as crawfish) for the presence of chloramphenicol. FDA is taking this action because low levels of chloramphenicol have been detected by some states and other countries in imported shrimp and crayfish.

"The FDA is concerned about any detection of chloramphenicol in shrimp and crayfish," said Dr. Lester M. Crawford, FDA Deputy Commissioner." The Agency will take whatever action is necessary to protect the public health."

The Center for Veterinary Medicine has played an integral role in responding to the discovery by the European Union (EU) and Canada of chloramphenicol in imported honey and shrimp from China. The Center is working with FDA's Office of Regulatory Affairs (ORA) and Center for Food Safety and Applied Nutrition (CFSAN) to prevent honey and shrimp contaminated with chloramphenicol from entering the U.S.

Scientists at CVM's Office of Research are investigating new approaches for the detection of chloramphenicol in honey and shrimp. Part of the effort involves the evaluation of a commercially available rapid screening kit for chloramphenicol. The manufacturer recently improved the kit to be able to detect 0.3 parts per billion (ppb) in honey and 0.15 ppb in shrimp. The screening kit will be used to determine which samples likely contain chloramphenicol and require additional testing.

Photo by Renate Reimschuessel

CVM chemists are evaluating triple quadrupole mass spectrometry for the confirmation of chloramphenicol residues in shrimp and honey.

The methods used to confirm the presence of chloramphenicol in shrimp and honey are also being evaluated and validated. Using sophisticated liquid chromatography tandem mass spectrometry techniques, Office of Research scientists are testing methods that can confirm the presence of chloramphenicol at concentrations of 0.1 ppb. When these evaluations have been successfully completed, the validated methods will be transferred to ORA laboratories for use as part of the program to test imported products for chloramphenicol residues.

"The FDA is concerned about any detection of chloramphenicol in shrimp and crayfish," said Dr. Lester M. Crawford, FDA Deputy Commissioner. "The Agency will take whatever action is necessary to protect the public health."

Until recently, the sensitivity of the methodology prevented the detection of chloramphenicol in shrimp below 5 ppb. Canada and the EU have refined their methods to detect even lower levels and have taken action on food products from China and Vietnam found to be contaminated by chloramphenicol.

The FDA has modified its methodology to confirm chloramphenicol levels in shrimp and crayfish to 1 ppb and is further modifying the methods to detect 0.3 ppb, which will place the U.S. methodology in line with Canada's and the EU's.

(Continued, next page)

FDA VETERINARIAN

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Rockville, MD 20855

FDA INCREASES SAMPLING . . . (Continued)

On June 5-6 2002, a senior delegation of Chinese officials met with FDA to discuss the issue of chloramphenicol residues in shrimp and crayfish. The delegation informed FDA that on March 5, 2002, China banned the use of chloramphenicol in animals and animal feeds. They also informed FDA that they are initiating testing of shrimp, crayfish, and other animal derived foods intended for export to ensure the absence of chloramphenicol and other drug residues. FDA and China exchanged information on testing methodologies. FDA informed the Chinese officials that the Agency would take enforcement action against violative product.

The FDA continues to work with other governments and state agencies to ensure the safety of the U.S. food supply.

CATHY BECK JOINS SENIOR TEAM

The Center for Veterinary Medicine (CVM) has recently reorganized the Office of the Center Director. Ms. Cathy Beck, formerly with FDA's Office of the Commissioner, is the new Associate Director for Executive Programs.

With 28 years of service with FDA and HHS, Ms. Beck has served as the Director of the Executive Secretariat at FDA, and as the Deputy Director of the Executive Secretariat at HHS. Ms. Beck's knowledge of the Agency and how it operates, her numerous contacts at both the Agency and the Department, and her direct experience in organizing and directing Executive Secretariat offices make her ideally suited for this new position in CVM.

Cathy Beck with friends, Paddy and Murphy.

Ms. Beck will oversee the following functions and staffs at CVM: Ombudsman, Advisors and Consultants, including Veterinary Medicine Advisory Committee (VMAC), Project Management, and Communications.

In addition, Ms. Beck is currently establishing an Executive Secretariat to serve as the major Center-level focal point for all inquiries, requests, and correspondence directed to the Center Director related to Center-wide programs.

CVM ISSUES GUIDANCE ON USE OF CLOVE OIL AND EUGENOL FOR FISH

FDA's Center for Veterinary Medicine (CVM) has issued level 2 guidance that provides information regarding the use of clove oil and its components for the anesthesia of fish. This Guidance for Industry, "Status of Clove Oil and Eugenol for Anesthesia of Fish" (Guidance # 150), is posted on the CVM Home Page at: *http://www.fda.gov/cvm/guidance/published.htm*. Single copies of the Guidance may be obtained by writing to the *FDA Veterinarian*. Please send one self-addressed adhesive label to assist in processing your request.

Clove oil is actually a mixture of different compounds. The three significant active ingredients are eugenol, isoeugenol and methyleugenol. Clove oil is 85 to 95% eugenol. Isoeugenol and methyleugenol make up 5 to 15% of the remaining ingredients. Neither clove oil nor any individual active ingredient of clove oil (eugenol, isoeugenol, or methyleugenol) is approved for use for the anesthesia of fish. Therefore, the use of either clove oil or eugenol as an

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CVM ISSUES GUIDANCE ON USE OF CLOVE OIL AND EUGENOL FOR FISH (Continued)

anesthetic for fish makes them unapproved new animal drugs.

This Guidance document includes information about anesthetic choices for use in fish, human food safety of clove oil and its active ingredients, a publicly disclosable Investigational New Animal Drug (INAD) Exemption file for isoeugenol as a fish anesthetic, and use of investigational drugs in a laboratory setting.

This Guidance document does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used as long as it satisfies the requirements of the applicable statute and regulations.

Comments and suggestions regarding this Guidance document should be submitted 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 the exact title of the document.

. . . the use of either clove oil or eugenol as an anesthetic for fish makes them unapproved new animal drugs.

For questions regarding information about the drug approval process and INAD files, contact Dr. Joan Gotthardt, Center for Veterinary Medicine (HFV-130), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7571.

For questions regarding information about regulatory discretion, contact Ms. Fran Pell, Center for Veterinary Medicine (HFV-235), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-0188.

NATIONWIDE RECALL OF MIRACLE LEG PAINT

CVM received a telephone call from the Veterinary Diagnostic Laboratory, Auburn, Alabama, concerning the death of a horse following application of a mercuric chloride blistering agent to the legs. The use of mercury blistering agents to treat lameness in horses is outdated, unsafe for animals and humans, and outside the scope of modern veterinary medicine.

The Miracle Leg Paint was purchased from the Equine Miracle Corporation in Grapeland, Texas. Mercury compounds in human drug products were prohibited following a notice in the *Federal Register*, Vol. 63, No. 77, April 22, 1998. All mercury-containing products were subject to removal from the market place in order to reduce human exposure and safeguard the public health regardless of the source of mercury in pharmaceuticals or medical devices.

On May 30, 2002, Equine Miracle Corp, agreed to a nationwide voluntary Class I Recall of Miracle Leg Paint, and agreed to stop manufacturing the product.

On June 17, 2002, CVM received another Adverse Drug Event Report from Louisiana State University, Veterinary Teaching Hospital. A horse became frantic and maniacal and was euthanized shortly after admission to the Veterinary Teaching Hospital. Heavy metal poisoning was suspected and toxicology tests revealed 240 ppm of mercury in the kidney, confirming mercury poisoning. The owner admitted to using Miracle Leg Paint on the horse every two weeks since November 2001.

There are no approved veterinary drug products that contain mercury as an active ingredient, and the use of mercuric blistering agents is not generally recognized as safe and effective. There are safety concerns for humans handling products containing mercuric chloride blistering agents. Poisoning and death have occurred in humans after applying the mercuric chloride products to large areas of the skin.

The product, administered topically on horses for the treatment of lameness, shin bucks, bows, chips, splints, and other horse leg ailments, was distributed nationwide to veterinarians, dealers, and consumers. All Miracle Leg Paint remaining on the market is subject to this recall.

Consumers who have purchased this veterinary drug are urged not to use it but to instead destroy the product by contacting their local waste management services and determining appropriate methods of destruction for this toxic product. Consumers with questions may contact Equine Miracle Corp. at 1-936-687-2800.

FDA LEVERAGING INITIATIVE IN LINE WITH PRESIDENT'S MANAGEMENT AGENDA

by David Batson, Ph.D. and Melissa Starinsky

Introduction

This is the first in a series of articles that will discuss some of the current and planned leveraging activities in the FDA's Center for Veterinary Medicine (CVM). The purpose of these articles is to stimulate an interest in and to inform Center stakeholders, our employees, and other interested parties about how to pursue leveraging opportunities within CVM.

The impact of Federal government downsizing, the changing economy, technological advances, and other factors, have prompted the Food and Drug Administration (FDA) to re-examine how it operates and to continuously seek out partnering opportunities to maximize the use of its resources.

What is Leveraging?

Over the last few years the FDA has emphasized the notion of collaborating or partnering with outside parties as a primary strategy to more effectively accomplish its mission of promoting and protecting the public health. This concept of collaboration and partnership in FDA is generally known as "leveraging." The President's Management Agenda (PMA) reinforces this concept through an emphasis on public-private partnerships and statements such as "We must have a Government that thinks differently . . . ." Through implementation of the PMA, the Agency will strive to increase leveraging opportunities with the private sector and others.

Why leverage?

It makes good business sense to engage in relationships where collaborators work synergistically to achieve goals that neither party could achieve on its own. Examples include joint workshops to assess particular public health challenges, co-sponsored training sessions, consensus standard setting, and mission-related research.

FDA/CVM has worked with outside groups for decades. In the early 1970's, under Commissioner Edwards, FDA expanded its use of outside advisory committees to harness the knowledge of experts outside the Agency to maximize the quality of certain product reviews. Although the FDA has a long history of collaborating with the external scientific community through cooperative agreements, interagency agreements, memorandums of understanding, and cooperative research and development agreements, it is now striving to make leveraging one of the core components of its operations. In fact, CVM believes so strongly in the benefits and value of collaboration that it has recently added leveraging as a core competency for all of its employees. As a result, leveraging has received increased emphasis and support by upper management, and training opportunities will be offered to all Center employees to develop the skills necessary for increasing leveraging partnerships in CVM.

It makes good business sense to engage in relationships where collaborators work synergistically to achieve goals that neither party could achieve on its own.

How does FDA leverage?

All of the FDA/CVM partnerships have arisen from the initiative, creative thinking and ideas of our outside stakeholders, front-line employees, managers, and others. It is from these ideas that formal agreements and informal collaborative relationships have flourished. A number of factors will determine the formality of the agreement required including the collaborator, whether FDA funds are to be committed, and whether intellectual property rights may arise from the collaboration. Formal agreements may include:

- **Cooperative Agreement** – This involves a collaborative effort between the FDA and the partner in which substantial technical expertise is anticipated between both parties and FDA will provide at least part of the funding for the project.
- **Cost-Sharing Contract** – A cost-sharing contract is one under which the Federal Government contracts for goods or services and the contractor absorbs a portion of the total cost of the effort. These arrangements are usually appropriate when the contractor is able to apply or market the developed product for the benefit of their business.
- **Cooperative Research and Development Agreement (CRADA)** – CRADAs involve collaborative

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FDA LEVERAGING INITIATIVE IN LINE WITH PRESIDENT'S MANAGEMENT AGENDA (Continued)

efforts between the FDA and one or more partners (academia, industry, not-for-profit, for-profit, State and local government organizations). From the FDA perspective, the CRADA is intended to help develop FDA technology, inventions, training programs, etc., that will facilitate achievement of mission-related goals. The CRADA partner, in return, receives some benefit from the establishment of this collaboration. The CRADA partner may provide funds to be used for the CRADA project. FDA and the partner may each contribute staff time and expertise, equipment, supplies, and facilities. Both parties are expected to make significant intellectual contributions to the objectives of the project.

- **INTER-AGENCY AGREEMENT (IAG)** – The purpose of the collaboration is the sharing of knowledge, personnel or other resources to strengthen programs of mutual concern between two or more Federal agencies. It is also used as a mechanism for eliminating overlap or duplication of effort. Within the framework of the IAG, the parties may either contribute or receive funds, services, staff, property, facilities, equipment, or exchange information to forward the common project goal.
- **CO-SPONSORSHIP AGREEMENT** – This can involve activities such as the joint development of a conference, seminar, symposium, educational program, or public information campaign that is related to the mission of the Agency. This kind of cooperative agreement involves the FDA and one or more non-Federal entities that share a mutual interest in the subject matter. As part of this cooperation, each party provides its own funding or staffing.

It is critical to emphasize the importance of bringing potential leveraging opportunities to the attention of FDA/CVM program personnel or CVM Leveraging Points of Contact (see information at end of article) for consideration. After the idea or concept is discussed and a decision made with respect to moving forward, the appropriate mechanism for implementing the collaboration can be determined.

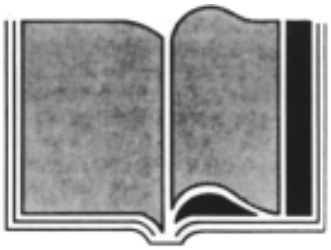
Additional information on how the FDA/CVM leverages will be available in upcoming articles and is currently available in FDA's Leveraging Handbook, which is available on the FDA web site *http://www.fda.gov/oc/leveraging/default.htm*

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.

PUBLICATIONS AVAILABLE

FDA Fact Sheets Available in Spanish



Thirteen Fact Sheets published by FDA are now available electronically in Spanish. The Fact Sheets describe how FDA protects the public health, regulates products including foods, drugs, medical devices, veterinary medicines, blood products, and other important products Americans depend on every day.

The Fact Sheets are easily accessible on FDA's Home Page at *www.fda.gov* by clicking on *Fact Sheets*. Fact Sheets available in Spanish are followed by the words "Spanish version" in bold. The Spanish language versions are in HTML and PDF formats.

The Fact Sheets translated include "FDA Fights Rare Diseases: New Help for Patients Without Treatments," Improving Public Health, Promoting Safe and Effective Drug Use," and "Keeping the Nation's Food Supply Safe: FDA's Big Job Done Well."

Other Fact Sheet topics describe the regulation of medical devices, adverse event reporting, protecting human subjects in clinical trials, safeguarding animal health and keeping the U.S. free of "Mad Cow" disease, FDA's role in regulating imports, and a description of domestic field operations.

CVM OMBUDSMAN ANNUAL REPORT 2001

by Marcia Larkins, D.V.M.

Background

The Ombudsman position was established in the Center for Veterinary Medicine (CVM) in November of 1999. The CVM Ombudsman 1) handles complaints and helps to resolve disputes involving science and policy issues for products regulated by CVM and 2) is a point of contact for response to inquiries and requests for general information and for information on specific issues involving science, policy and procedures or for referral to the appropriate resource within the Center. Additionally, the Ombudsman advises the Office of the Center Director (OD) concerning any trends in the recurrence of specific issues or problems that may have an impact on Center policy and makes recommendations for change or improvement.

This report provides an overview of the Ombudsman's activities for the calendar year 2001.

General Categories and Subjects

The complaints and inquiries handled by the CVM Ombudsman during 2001 can be categorized generally as: complaints concerning specific products that were approved by or granted regulatory discretion by CVM; complaints/comments about existing FDA/CVM policies or administrative procedures and their impact on the public, academia, research, and private industry; inquiries and questions about FDA policy regarding specific issues/products; and requests for general information on the review/approval process. These categories covered the following subjects/areas:

- Approved veterinary drugs
- Contacts/resources in FDA/CVM and other Agencies
- Cooperative Research and Development Agreement (CRADA)
- CVM Home Page
- CVM policy/administrative process
- INADs/NADAs
- Drug exportation
- Drug Master File (DMF)
- Drug shortage/withdrawal
- Extra-label use policy (human and veterinary drugs)
- FDA personal import policy
- Freedom of Information (FOI) summary
- MOU
- Regulatory discretion
- Regulations and guidelines
- Veterinary colloid solutions
- Wildlife drugs
- VMAC

There were a total of 88 complaints and inquiries handled by the CVM Ombudsman during the 2001 calendar year, which is a 38% increase over the number for the year 2000. The majority (91%) of these originated outside the Center from consumers, scientists and other professionals, private industry and other Federal agencies. Only 9% of the inquiries originated from inside CVM or within FDA. However, several of the complaints or inquiries were referred to the Ombudsman from within CVM (28%), another Center Ombudsman (5%), and the Office of the FDA Ombudsman (1%). The Ombudsman was also contacted directly by e-mail, telephone and regular mail (66%).

Science and Policy

As stated above, the Ombudsman handles science and/or policy issues related to products regulated by CVM. The complaints and inquiries received during 2001 for the subjects/areas listed above, involved one or both issues as follows:

- Regulatory discretion process 55%
- Extra-label use requirements 10%
- Policy/administrative process 11%
- Pre-approval data requirements 6%
- Center contacts/resources for specific issues 3%
- Drug approval status 3%
- Import/export for approved/unapproved drugs 2%
- Post-approval issues 2%
- Archived VMAC information 2%

(Continued, next page)

CVM OMBUDSMAN ANNUAL REPORT 2001 (Continued)

- Enforcement of regulations versus guidelines 2%
- Drug shortage issues 1%
- Pending human drug approval 1%

The complaints and inquiries handled by the Ombudsman involved the Offices in CVM directly or indirectly as follows:

- Office of Surveillance & Compliance ..... 66% *(includes referrals from OMAC/ONADE /CDER)*
- Office of New Animal Drug Evaluation (ONADE) 22%
- Office of the Director (OD) 5%
- Office of Management and Communications (OMAC) 2%
- Other (outside CVM) 6%

The types of complaints/concerns (59% of total) received in relation to the science or policy issues were as follows * :

- Unavailability of or delays in getting veterinary drugs due to shortage or due to withdrawal of human drugs 52%
- High cost of drugs marketed under regulatory discretion 10%
- Timeliness in review/response to submissions, letters, phone calls or e-mails 8%
- Misinformation in veterinary publication ... 6%
- Delays in the approval process 4%
- Concern regarding possible retaliation 4%
- Use of unapproved drug by practicing veterinarian 2%
- Inconsistency between regulations and guidelines 2%
- Changes in policy during the review/approval process 2%
- FOI summary data and extra-label use 2%
- Data requirements 2%
- High cost of veterinary drugs inside as compared to outside the U.S. 2%

* individual complaint may represent more than one party

Resolution of Complaints and Inquiries

Of the 88 complaints and inquiries received by the Ombudsman 88% were resolved or referred while 13% are either pending or unresolved as follows:

- handled directly by the Ombudsman 73%
- follow-up action by Center staff 10%
- referred to CVM staff, other Center or other Agency 5%
- follow-up still pending 1%
- unresolved 11%

Systemic Issues

Overall, the complaints and inquiries received/handled by the Ombudsman reflected primarily four systemic issues as follows:

1. **Regulatory/enforcement discretion process**

   Many of the questions and complaints (55%) involved some aspect of the regulatory/enforcement discretion process. This issue is a carry-over from the year 2000, and it increased by 7% in 2001. Human drugs used in veterinary medicine have been withdrawn from the market and approved veterinary drugs have become unavailable for various reasons such as evidence of adverse reactions, manufacturing problems, and marketing decisions. The withdrawal of drugs approved for humans that are also used by veterinarians to treat conditions in animals that are life-threatening or where the lack of treatment results in a serious negative impact on the animal's quality of life, has been increasing for several years. These drugs have become unavailable with little or no warning leaving veterinarians and pet owners frantic for alternative resources. The owners dreaded the idea of having to consider euthanasia for a treasured pet that with proper treatment could live a fairly normal life. The drugs may have been removed from the market by the FDA based on evidence of life-threatening

(Continued, next page)

CVM OMBUDSMAN ANNUAL REPORT 2001 (Continued)

adverse reactions in humans or by the sponsor based on adverse reactions or due to certain marketing considerations.

2. **Timeliness in response to data submissions, letters, phone calls or e-mails**

   This issue is also a carry-over from the year 2000 and the incidence remained about the same in 2001. The complainants' primary concerns were the lack of response to direct inquiries about the status of a current submission and after a specific timeframe or due date had passed.

3. **Approval Process**

   Complainants expressed frustration in moving things through the approval process in general and because of changes in definitions and in policy based on "new information" that occur repeatedly during the review process in spite of prior documented commitments.

4. **Retaliation**

   While there were no direct accusations of retaliation, the complainants expressed reluctance to pursue resolution of their issues even via an informal process due to concerns that it might impact the handling of current and/or future submissions. The Ombudsman's page at the CVM web site includes information on the Agency's policy on retaliation and how to report it.

Dr. Larkins is CVM's Ombudsman.

NEW VERSION OF BSE INSPECTION CHECKLIST RELEASED

FDA's Center for Veterinary Medicine (CVM) has released a new version of the Bovine Spongiform Encephalopathy (BSE) Inspection Checklist *http://www.fda.gov/cvm/forms/BSE_V41.pdf*, that is available on the Center's Home Page on the Internet. This checklist is to be used by all Federal and State inspectors to determine compliance with FDA's ruminant feed (BSE) regulations, *Code of Federal Regulations*, Title 21, Part 589.2000 *http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr589_01.html*. This newest checklist version coincides with the release of a new database module that will record the results of all inspections conducted under this regulation.

This regulation that prohibits the use of most mammalian protein in feeds for ruminant animals was implemented to prevent the establishment and amplification of BSE through feed in the United States. The rule became effective on August 4, 1997. Inspections of more than 13,000 renderers, feed mills, ruminant feeders, and others (such as protein blenders) have been conducted to determine compliance with the BSE feed regulations. The majority of these inspections (around 80%) were conducted by State officials, and the remainder by FDA. A checklist has been used to record information on the compliance with the rules. This newly revised checklist supercedes all previous versions, and should be used in future inspections.

Questions or comments about the checklist may be directed to Dr. Neal Bataller in CVM's Division of Compliance at: *<Nbatalle@cvm.fda.gov>*, 301-827-0163.

INFORMATION ON REGISTRATION FOR FOREIGN ANIMAL DRUG ESTABLISHMENTS

A final rule that became effective on February 11, 2002, requires owners of foreign animal drug establishments to designate a U.S. agent for purposes of registration and drug listing. The establishment needs to identify their U.S. agent **in writing**. This letter should be on the firm's letterhead, signed by an official of the firm, and mailed to the following office:

FDA/CDER/Drug Reg. and Listing
5600 Fishers Lane (HFD-095)
Rockville, MD 20857

Additional information about the final rule that amended Title 21, Part 207, of the *Code of Federal Regulations*, may be found in the November 27, 2001, *Federal Register* (*<http://www.fda.gov/OHRMS/DOCKETS/98fr/112701a.htm>*) and in a December 5, 2001, CVM UPDATE (*http://www.fda.gov/cvm/index/updates/foreignup.htm*). Further information on animal drug registration and listing may be obtained from Lowell Fried, FDA/Center for Veterinary Medicine, HFV-212, 7500 Standish Place, Rockville, MD 20855, telephone number 301-827-0165, e-mail *lfried@cvm.fda.gov*.

CVM SCIENTISTS WIN AWARDS

At the 2002 FDA Scientific Achievement Awards Ceremony, held on February 21, 2002, the following CVM scientists were recognized:

Excellence in Analytical Science

Raafat Fahmy, Ph.D. – *For excellence in developing novel methods for the dissolution of aspirin, sulfas and tetracycline boluses, a unique dosage form, using standard USP apparatus and environmentally sound solvents.*

Dr. Raafat Fahmy

Excellence in Laboratory Science

Patrick F. McDermott, Ph.D. – *For demonstrating the impact the use of fluoroquinolones in chickens has on the selection for fluoroquinolone resistant* Campylobacter.

Dr. Patrick F. McDermott

Excellence in Review Science

Tania Denise Woerner, V.M.D. – *Dr. Woerner utilized a novel approach to corroborate the findings of a clinical study for the approval of ponazuril to treat Equine Protozoal Myeloencephalitis (EPM).*

Dr. Tania Denise Woerner

Outstanding Inter-Center Scientific Collaboration

Phenylbutazone Residue Group – ORA

Denver District Laboratory

Karen S. Kreuzer
Mark R. Madson
Sherri B. Turnipseed, Ph.D.
Susan B. Clark
Gene J. Nandrea
William B. Martin, Ph.D.
W. Douglas Rowe
Lara L. Murphy
John N. Sofos

Seattle Regional Laboratory

Jeffrey A. Hurlbut, Ph.D.

CVM

Deborah A. Cera
John O'Rangers, Ph.D.
Michael H. Thomas
Mary C. Carson, Ph.D.
David N. Heller

For protection of the Public's Health through the reduction of Phenylbutazone abuse in food-producing animals through analytical surveillance, education and regulatory actions.

CVM is proud of these accomplishments and congratulates all FDA award winners.

GUIDANCES AVAILABLE ON FELINE AND POULTRY ANTHELMINTIC EFFECTIVENESS

The Food and Drug Administration (FDA) is announcing the availability of two final guidances for industry entitled "Effectiveness of Anthelmintics: Specific Recommendations for Feline" (Guidance #113) and "Effectiveness of Anthelmintics: Specific Recommendations for Poultry-*Gallus gallus*" (Guidance #114).

These related guidance documents have been developed by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). They are intended to standardize and simplify methods used in the evaluation of new anthelmintics submitted for approval to the European Union, Japan, and the United States.

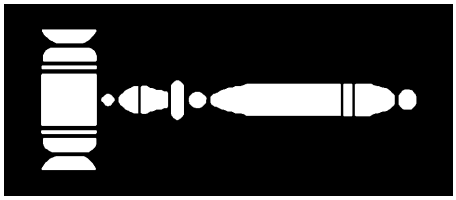
Guidance documents 113 and 114 are posted on the FDA/Center for Veterinary Medicine Home Page at: *http://www.fda.gov/cvm/guidance/published.htm#documents*. Single copies of the guidance may be obtained by writing to the *FDA Veterinarian*. Please send a self-addressed adhesive label to assist in processing your request.

Written comments on the guidance may be submitted at any time to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Electronic comments may be submitted to *http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm*. Comments should be identified with the full title of the guidance document and Docket number 00D-1629.

Additional information on the guidance documents may be found in the June 25, 2002, *Federal Register* (*http://www.fda.gov/OHRMS/DOCKETS/98fr/062502h.htm*) and from Dr. Thomas Letonja, Center for Veterinary Medicine (HFV-135), Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-7576, e-mail: *tletonja@cvm.fda.gov*.

REGULATORY ACTIVITIES

by Karen A. Kandra



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

- Brent J. Rus, Owner, Brent Rus Farm, Rock Valley, IA
- Mike G. Vierstra, Owner, Vierstra Dairy, Twin Falls, ID

These violations involved illegal residues of penicillin, gentamicin, and sulfamethazine in a cow, and multiple residues of tilmicosin and penicillin in dairy cows.

The following individuals/firms received warning letters for violations related to 21 CFR Part 589.2000 – Animal Proteins Prohibited in Ruminant Feed. This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy (BSE):

- Jeffrey T. Buck, Owner, All American Feed & Tractor, Sandpoint, ID
- Kenneth M. Van Dyke, President, Van Dyke Grain Elevators, Inc., North Plains, OR
- Philip C. Anderson, General Manager, Darling International, Inc., Tacoma, WA

Violations included failure to maintain sufficient records and written procedures to prevent cross-contamination; failure to keep written procedures for cleaning out or flushing equipment after mixing feeds containing prohibited material; failure to provide written procedures for separating products that contain or may contain prohibited material from ingredients used in ruminant feeds, from the time of receipt until the time of shipment; and, failure to label meat and bone meal with the required cautionary statement "Do Not Feed to Cattle or Other Ruminants."

The following material was presented as a poster at the 102nd American Society of Microbiologists meeting in Salt Lake City, May 2002.

Humans as a Reservoir of Antibiotic Resistance Genes for Animals: Evidence of Antibiotic Resistance Gene Exchange Between Human and Animal Enterococci

by Simjee S, White DG, McDermott PF, Wagner DD and Walker RD

There have been several worldwide studies documenting the relatedness of vancomycin resistant *Enterococcus faecium* (VREF) isolates and a Tn1546 element, which confers glycopeptide resistance, found in animals and humans. Recently, 24 Tn1546 types were described from Europe and the United States. Some types were specific to human or animal VREF isolates, while others were common to both human and animal VREF isolates. Of the 24 VREF Tn1546 types two specific forms of Tn1546 (designated F1 and F2) are unique to human VREF isolates found only in the USA (Figure). In isolates unique to the United States, Tn1546 shows a deletion of 889 bp in ORF1and an insertion of IS1216V. In addition there is an insertion of IS1251 between *vanS* and *vanH*. The only difference between F1 and F2 types is a single base change, $C_{9692} \rightarrow T$.

Epidemiological studies from Europe suggest that VREF are horizontally transmitted from animals to humans. However, there have been no reports of high-level vancomycin resistance (>32 µg/ml) in *E. faecium* from animals in the United States. In view of the possible involvement of companion animals in the spread of antibiotic resistant enterococci to humans, we conducted a study to characterize gentamicin and vancomycin resistance among enterococci isolated from dogs presented with urinary tract infections at the Veterinary Teaching Hospital at Michigan State University over a two-year period (1996-1998).

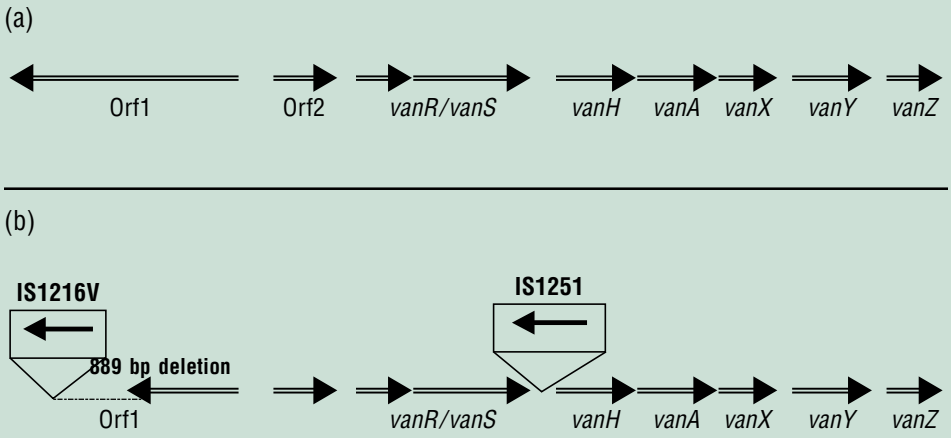
The potential role that companion animals may play in the dissemination of genes conferring clinically relevant resistance among enterococci requires further study.

Isolated species included *E. faecium* (n=13), *E. faecalis* (n=7), *E. gallinarum* (n=11), and *E. casseliflavus* (n=4). We found a single canine *E. faecium* isolate that showed both high level aminoglycoside and high level vancomycin resistance. Gene transfer experiments concluded that the vancomycin and gentamicin resistance genes were transferable independently of each other, ruling out the possibility of gene linkage. When we further characterized the vancomycin resistance determining elements we found that the *vanA* gene was part of Tn1546. Detailed molecular analysis of Tn1546 showed it to be

(Continued, next page)

FIGURE

Genetic Map of (a) Tn1546 and (b) Tn1546 Type F1 and F2 "USA Only Version"



Humans as a Reservoir of Antibiotic Resistance Genes for Animals . . . (Continued)

identical to the F1 type described above and shown in the Figure.

To determine whether this isolate was a canine *E. faecium* clone or a human VREF clone we conducted pulsed field gel electrophoresis (PFGE) studies. When we compared the canine VREF PFGE pattern to more than 63 different human VREF PFGE types no match was found. However, a match was found with another, non-VREF, canine *E. faecium* isolate that displayed high level gentamicin resistance but was susceptible to vancomycin. This would lead us to conclude that the canine VREF is indeed a canine *E. faecium* clone that has acquired the Tn1546 from an external source.

Several speculations can be made as to how a canine *E. faecium* strain may have acquired a Tn1546 that, to date, has only been described in VREF isolated from humans in the United States. Although direct selection pressure would be the most likely cause of acquisition of Tn1546, there is no record of the dog being administered vancomycin for treatment of its UTI. Additionally, it may be possible that either the dog owner or a member of the veterinary hospital staff attending to the dog was the source of the bacterium carrying the VREF transposon. Although this seems like a feasible route, no samples from either the dog owner or attending hospital staff are available for analysis.

These data demonstrate that exchange of resistance determinants between human and canine enterococcal strains can occur.

In summary, we have described the first U.S. report of a Tn1546 transposon in a VREF canine isolate that is indistinguishable from Tn1546 found in VREF human isolates. These data demonstrate that exchange of resistance determinants between human and canine enterococcal strains can occur. The potential role that companion animals may play in the dissemination of genes conferring clinically relevant resistance among enterococci requires further study.

NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 141-124)	Nicarbazin, Narasin, Bacitracin Methylene Disalicylate (Maxiban plus BMD®)	Broiler Chickens. For the prevention of coccidiosis and as an aid in the prevention of necrotic enteritis caused or complicated by *Clostridium* spp. or other organisms susceptible to bacitracin.	**MEDICATED FEED**—The NADA provides for using approved two-way narasin/nicarbazin and single-ingredient bacitracin methylene disalicylate Type A medicated articles to make three-way, combination drug Type C medicated feeds for broiler chickens. The Type C feeds are used for the prevention of coccidiosis caused by *Eimera tenella, E. necatrix, E. acervulina, E. maxima, E. brunetti*, and *E. mivati*. *Federal Register* 05/06/02

(Continued, next page)

NEW ANIMAL DRUG APPROVALS (Continued)

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Alpharma, Inc. (NADA 141-154)	Robenidine Hydrochloride, Bacitracin Methylene Disalicylate (Robenz® plus BMD®)	Broiler and fryer chickens. For the prevention of coccidiosis and as an aid in the prevention or control of necrotic enteritis.	**MEDICATED FEED:** The NADA provides for use of approved single-ingredient Bacitracin methylene disalicylate (BMD) and robenidine hydrochloride Type A medicated articles to make two-way combination Type C medicated broiler and fryer chicken feeds. The combination Type C medicated feeds are used for prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati,* and *E. maxima*. *Federal Register* 05/07/02
Schering-Plough Animal Health (NADA 141-190)	Diclazaril, Bacitracin Methylene Disalicylate, Roxarsone (Clinacox plus BMD® plus 3-Nitro®)	Broiler chickens. For the prevention of coccidiosis, as an aid in the prevention or control of necrotic enteritis, for increased rate of weight gain, improved feed efficiency, and improved pigmentation.	**MEDICATED FEED**—The NADA provides for use of approved single-ingredient diclazuril, bacitracin methylene disalicylate, and roxarsone Type A medicated articles to make 3-way combination drug Type C medicated feeds for broiler chickens. The Type C medicated feeds are used for the prevention of coccidiosis caused by *Eimeria tenella, E. necatrix, E. acervulina, E. brunetti, E. mivati*, and *E. maxima*. *Federal Register* 05/16/02
Alpharma, Inc. (NADA 141-185)	Decoquinate, Chlortetracycline (Deccox® plus Aureomycin®)	Calves, beef, and non-lactating dairy cattle. For the prevention of coccidiosis, treatment of bacterial enteritis, and treatment of bacterial pneumonia.	**MEDICATED FEED**—The NADA provides for use of approved decoquinate and chlortetracyline Type A medicated articles to make two-way combination Type B and Type C medicated feeds for calves, beef, and nonlactating dairy cattle. The combination Type C feeds are used for the prevention of coccidiosis caused by *Eimeria bovis* and *E. zuernii*, for the treatment of bacterial enteritis caused by *escherichia coli*, and for treatment of bacterial pneumonia caused by *Pasteurella multocida* organisms susceptible to chlortetracycline. *Federal Register* 05/23/02

SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Monsanto Co. (NADA 140-872)	Sometribove Zinc (Posilac 1 Step®)	Dairy cows. To increase the production of marketable milk with no restriction on injection site.	**SUBCUTANEOUS**—The supplement provides for subcutaneous injection with no restriction on injection site. Three sites are recommended: the neck area, the postcapular region, or the depression on either side of the tailhead. *Federal Register* 04/15/02
Elanco Animal Health Division of Eli Lilly & Co. (NADA 141-064)	Tilmicosin (Pulmotil®) Rx	Swine. For the control of swine respiratory disease associated with certain bacterial organisms.	**MEDICATED FEED**—The supplement provides for additional use information in labeling. The expiration date of Veterinary Feed Directives (VFD's) for tilmicosin must not exceed 90 days from time of issuance. VFD's for tilmicosin shall not be refilled. Do not use in Type B or C medicated feeds containing bentonite. Do not allow horses or other equines access to feeds containing tilmicosin. *Federal Register* 05/02/02
Pharmacia & Upjohn Co. (NADA 97-505)	Lincomycin (Lincomix 20 & 50)	Swine. For the control of porcine proliferative enteropathies (ileitis).	**MEDICATED FEED:** The supplement provides for use of Lincomix 20 and 50 feed medications in medicated swine feeds for the control of porcine proliferative enteropathies (ileitis) caused by Lawsonia intracellularis. *Federal Register* 05/24/02

ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Phoenix Scientific, Inc. (ANADA 200-293)	Furosemide (Furosemide Injectable 5%) Rx	Horses, cattle, dogs, cats.	**INTRAMUSCULAR or INTRAVENOUS**—The ANADA is a generic copy of Intervet, Inc.'s Lasix, approved under NADA 34-478. *Federal Register* 04/15/02
Alpharma, Inc. (ANADA 200-274)	Lincomycin, Lincomycin Injectable 30%	Swine. For the treatment of infectious arthritis and mycoplasma pneumonia.	**INTRAMUSCULAR**—The ANADA is a generic copy of Pharmacia & Upjohn Co's Lincomix 300, approved under NADA 34-025. *Federal Register* 05/14/02

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