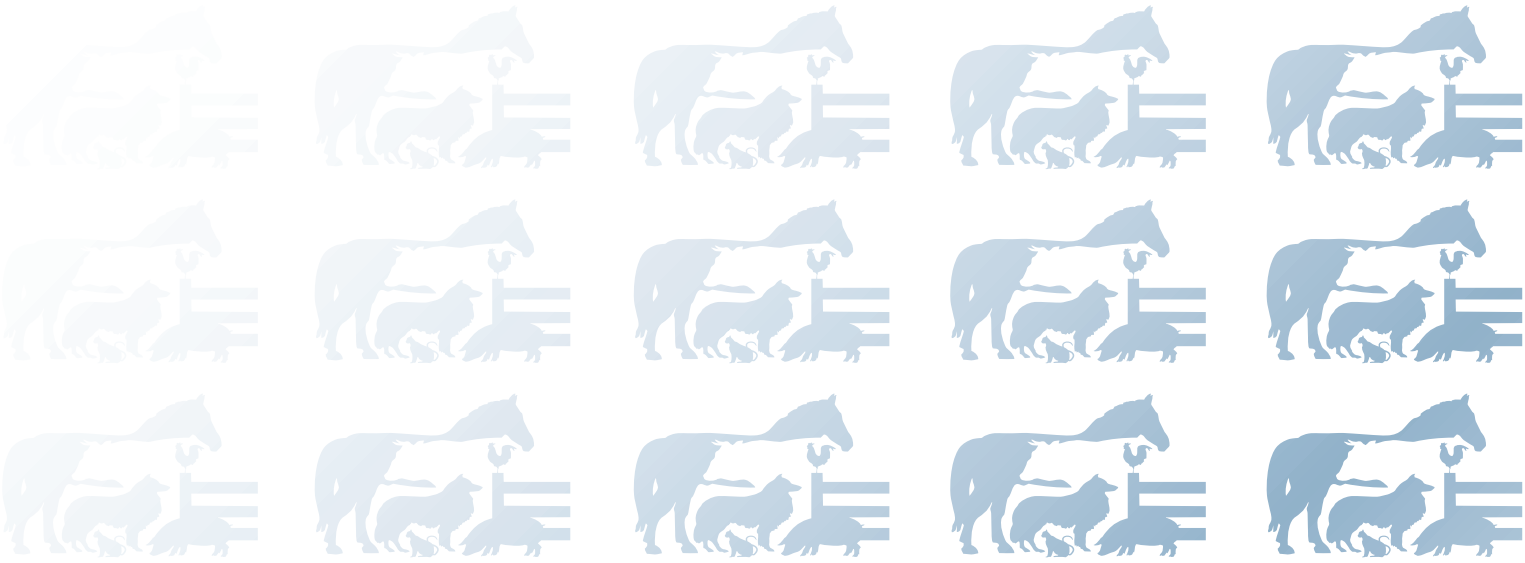

THE CENTER FOR VETERINARY MEDICINE

ANNUAL REPORT

Fiscal Year 2005: *October 1, 2004–September 30, 2005*

FDA: Celebrating a Century of Progress in the Regulation of Drugs and Food

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Contents

APPENDICES

Food and Drug Regulation Through the Years

1906 ..... *Congress passed the original Food and Drug Act. The Act's scope included animal feed and drugs for use in animals. The U.S. Department of Agriculture's (USDA) Bureau of Chemistry administered the Act.*

1927 ..... *USDA transferred the food and drug regulatory functions into a new Food, Drug, and Insecticide Administration (the name was changed to Food and Drug Administration in 1930). The Agency employed its first veterinarian, to evaluate claims for vitamins and minerals, in 1927.*

1938 ..... *Congress passed the Federal Food, Drug, and Cosmetic Act, substantially expanding the scope of the 1906 Act.*

1940 ..... *The Food and Drug Administration was transferred from USDA to the Federal Security Agency.*

1953 ..... *The Federal Security Agency became the Department of Health, Education and Welfare (DHEW). (FDA became part of the Public Health Service within the Department in 1968, and DHEW became the Department of Health and Human Services in 1980.)*

1953 ..... *The Veterinary Medical Branch was created within FDA's Bureau of Medicine.*

1965 ..... *The Bureau of Veterinary Medicine was established.*

1984 ..... *The Bureau of Veterinary Medicine became the Center for Veterinary Medicine.*

Today, the Center for Veterinary Medicine is an internationally recognized public health organization responsible for the evaluation, approval, and surveillance of animal drugs, food additives, feed ingredients, and marketed animal devices. CVM works to increase the availability and diversity of safe and effective drug products that relieve animal pain and suffering, sustain their health, and improve animal productivity without compromising public health.

CVM – A Great Place To Work

On the basis of the results of a survey of FDA employees, the Center for Veterinary Medicine is a great place to work. FDA used the Gallup Q12 (12 question) employee survey this year to assess the work culture throughout the Agency. The results revealed that CVM scored significantly higher on the 12 questions than any other center or major FDA office. For example:

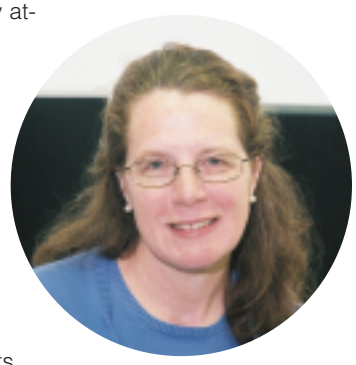
- Employee engagement (defined as those involved in and enthusiastic about their work) was 3.94 for CVM, compared with 3.66 overall for FDA (the maximum possible score was 5.0).
- The CVM score for satisfaction with the organization as a place to work was 3.90, compared with the overall Agency score of 3.64.

We have a very low turnover rate—the lowest of any FDA center. The following vignettes illustrate why CVM is a good place to work.

Returning to CVM

Ann Stohlman, D.V.M.

The Center's emphasis on science, combined with our managers' worker friendly attitude, brought Dr. Ann Stohlman back to work at CVM.



Dr. Stohlman came to CVM for the first time in 1998. Before that, she had a career working as a small animal veterinarian in Washington, D.C. After 13 years in the private practice, she came to work at CVM as an animal drug reviewer in the Office of New Animal Drug Evaluation (ONADE). Her focus was on products designed for treating pets.

At CVM, she said, she was impressed by the level of science used every day. Some "brilliant scientific minds" work at CVM, she said. She also liked the diversity in the types of professionals she worked with including other veterinarians, chemists, epidemiologists, and statisticians.

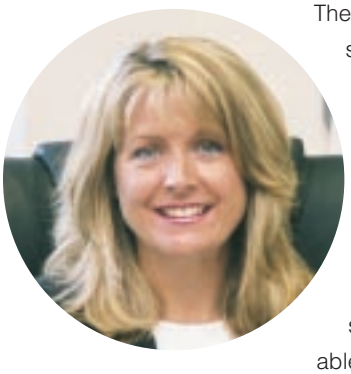
She appreciated the Center's family friendly attitude, Dr. Stohlman said. When a family emergency suddenly took her out of the office, her managers gave her the flexibility to take care of the problem, allowing her to work at convenient times and places.

Then, in 2001 she was offered a job as head of medicine at a veterinary clinic that would let her return to hands-on veterinary practice. She took the job and left CVM.

She loved working in the clinic, but she also missed the personal and professional benefits that came with employment at CVM, namely the camaraderie of working with a variety of scientists, and the sense of contribution that comes from making sure the drugs that reach the market are safe and effective.

Her solution was to return to the Center, again reviewing drugs for pets, while continuing to work part-time at the clinic. The work at the clinic keeps her in touch with the animals that are treated with the products she reviews.

Ms. Melissa Starinsky



The opportunity to help build CVM's Staff College brought contract and education specialist Melissa Starinsky back to the Center during FY 2005, after an 18-month hiatus working for private industry.

Ms. Starinsky has extensive contracting skills. After completing a government contracting intern program following college graduation, she became a Contracting Officer and an expert in acquisition and performance-based contracting for the Federal government. Having always had a passion for education, however, she made a career change, joining the Center in 1999 as a training specialist. The Center's family friendly policy was one of the attractions; she was able to work part-time at first, giving her flexibility to take care of a young family.

Ms. Starinsky was heavily involved in the development of CVM's Staff College, becoming the college's acting director. Her expertise was recognized outside the Center, though, and in November 2003 she joined the private sector to provide acquisition and performance consulting services to the Federal government. Her employer allowed her to work at home, giving her the flexibility she wanted to take care of her family.

She enjoyed the work as a consultant, but missed her experience at CVM's Staff College. She described the Staff College program as "innovative and cutting edge," not seen anyplace else either in government or the private sector. Also, she "really missed the decision-making authority" and the opportunity to get things done that her role at the Center offered – experiences that consulting did not offer. "CVM's management believes in a participatory decision-making process," she said.

So she returned to CVM in May 2005, and was named Staff College Director shortly thereafter. Ms. Starinsky said that she sees the Staff College as an embodiment of commitments the Center's management has made to its employees to help them grow professionally and provide a culture that fosters high performance. "The Center is doing a lot of things well," she said.

A MESSAGE FROM THE DIRECTOR

CVM Director, Dr. Stephen F. Sundlof

The year that has just passed brings to a close a century of food and drug regulation since the passage of the Food and Drug Act of 1906. Although the original Act provided regulatory authority over animal products, it did not authorize preclearance of animal drugs. We can measure the change that has occurred since 1906 in the accomplishments we report for this past year. Premarket approval of animal drugs for safety and effectiveness has now been taking place for well over half a century. Veterinarians and animal caretakers now have access to animal drugs that no one could have imagined possible in 1906. And now, at the cusp of the second century of drug regulation, we are implementing a program of user fees to expedite and improve the drug approval process. It is exciting to be a part of FDA's entry into its next century of protecting the public health.

CVM met all of its performance and financial goals under the Animal Drug User Fee Act (ADUFA) during FY 2004, the first year of the program. We worked diligently during FY 2005 to accomplish the ADUFA goals for this past year. For example, we worked with the FDA Office of Financial Management to ensure that the ADUFA funding is planned carefully, spent efficiently and tracked appropriately. We are using the increased resources from user fees to bolster our ability to review animal drug applications in a timely fashion. This means we are working against tighter deadlines each year, for example, 270 days to complete reviews of 90% of new animal drug applications in FY 2005, compared with 295 days in FY 2004.

A century after the beginning of food and drug regulation, we are able to implement special measures to provide drugs, for certain animals and uses, that might not be available through the normal approval process. That is, we moved ahead during the past year in implementing the Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act), which will significantly expand the availability of drugs for minor species and minor uses in major species of animals. For instance, we took major steps toward implementing the "designation" provisions of the MUMS Act, which provide incentives to drug sponsors for gaining approval for MUMS drugs.

Microbial resistance to antibiotics and other antimicrobial drugs was not on the regulatory radar screen at the beginning of the 20th century, because antibiotics were not yet in use in human and animal medicine. Things certainly have changed in 100 years. Last year, we took strides in several areas related to antibiotic resistance resulting from the use of antimicrobial drugs in animal medicine. Along with our partners – the U.S. Department of Agriculture and the Centers for Disease Control and Prevention – we continued to expand monitoring for antimicrobial resistance under the National Antimicrobial Resistance Monitoring System (NARMS). This included the development of an integrated NARMS Reporting System containing reliable and accurate data to help expedite the antimicrobial drug approval process, as well as to provide necessary post-approval monitoring information.

In June 2005, the international Codex Alimentarius Commission issued an expedited acceptance of a *Code of Practice to Minimize and Contain Antimicrobial Resistance* within the Codex Committee on Residues of Veterinary Drugs in Foods. A group chaired by the Center's then-Deputy Director, Dr. Linda Tollefson, drafted the document.

During the year, the Agency withdrew approval of enrofloxacin for use in poultry based on antimicrobial resistance concerns. FDA also published and reviewed comments on a draft risk assessment on the use of virginiamycin in animals; and continued the review of the antimicrobial safety of previously approved penicillin and tetracycline products.

Bovine spongiform encephalopathy (BSE) was not known in 1906, but BSE occupied much of our attention during the past year. The diagnosis of a second BSE-infected cow in the United States brought immediate compliance action by FDA to prevent the spread of BSE through animal feed. Because of the ramifications for international marketing of U.S. beef, representatives of our government met with representatives of foreign governments here and abroad, and CVM participated in the meetings. We also took steps, through issuance of a proposed regulation, toward implementing measures that would strengthen our 1997 feed regulation. That regulation is intended to prevent the establishment and amplification of BSE through feed. We list this regulation and other significant FY 2005 publications in Appendix A.

This annual report documents the Center's growing leadership and interaction in international issues related to animal drugs and feeds. For instance, CVM had an active role in the third International Cooperation on Harmonisation of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH) Conference, held in May 2005 and hosted by the U.S. delegation. VICH is an international program aimed at harmonizing the technical requirements for the registration or licensing of veterinary medicinal products. The "VICH3" conference focused on the numerous VICH guidelines that have been published in draft or final form during the last three years and marked the closure of the first phase of the harmonization of regulatory requirements among the VICH participating regions.

This year, we approved a number of new animal drug applications. A first of its kind approval was for Aquaflor® (florfenicol), an antimicrobial for control of mortality due to enteric septicemia in catfish. This was the first approval of a drug indication that we had designated under the MUMS Act, the second approved Veterinary Feed Directive drug, and the first new antimicrobial approved for finfish in over two decades. We also granted a number of other food animal drug approvals during the year. An example was the approval of Rumensin® (monensin sodium) for increased milk production efficiency in dairy cows. This is the first approval of a new animal drug feed ingredient that increases milk-production efficiency. An example from a number of nonfood animal approvals was the approval of REBALANCE (pyrimethamine and sulfadiazine), an antiprotozoal product indicated for the treatment of horses with equine protozoal myeloencephalitis caused by *Sarcocystis neurona*. Development of new drugs to treat companion animals is a positive economic trend in the animal drug industry. We list significant FY 2005 animal drug approvals in Appendix B.

FDA's Gallup Q12 survey has documented what we have suspected: CVM is a great place to work. As the vignettes in the preface illustrate, CVM ranked at the top among FDA components in employee satisfaction. We believe that this is due in part to the organization development model we have been following for several years – the High Performance Organization, or HPO. Being the "employer of choice" in government is one of the goals we identified through HPO.

The Deputy Director's message highlights achievements by individuals in the Center. We regret that Rear Admiral Linda Tollefson left the Center on September 15, 2005, but congratulate her on her appointment as Assistant Commissioner of Science in FDA. Her appointment is most appropriate considering her many achievements, including Agency-wide contributions, in the past. For example, Dr. Tollefson serves as chair of the FDA Commissioner's Advisory Committee on the Commissioned Corps. The committee's membership includes 17 members of the Corps, including all of FDA's top-ranking Corps officers, and two civilian supervisors of Corps officers.

We present more details on the Center's many accomplishments in this annual report. The following pages set out the challenges we face, and our accomplishments during the past year. As highlighted throughout this report, our performance goals are aligned with the President's Management Agenda, the Department of Health and Human Service

Secretary's 500-Day Plan, and the FDA Strategic Action Plan. Where we reached our performance goals for FY 2005, we have so indicated. Where we fell short of the goals, we have indicated this also. We believe we best serve the public by reporting our shortcomings along with our accomplishments.

The achievements we report resulted from the hard work of a competent and dedicated staff. This report also documents continued expansion of collaborative activities with many of our stakeholders and partners. These arrangements provide mutual benefit, and allow us to fulfill our role in protecting the public health more effectively and efficiently. We are grateful for the support of our stakeholders and partners as we work together for the public good.

A MESSAGE FROM THE DEPUTY DIRECTOR

CVM Deputy Director,
Dr. Linda Tollefson

I have the privilege of following Dr. Sundlof's summary of our substantive FY 2005 achievements with a report on developments in the organization that are behind the accomplishments.

The new laws discussed by the Director require organizational changes and recruitment of significant numbers of new staff. We met our goals for hiring new professional staff to review new animal drug applications under ADUFA, and we were pleased with the high caliber of those we were able to employ. As required by the MUMS legislation, we established a new Office of MUMS Animal Drug Development, which meant establishing the functional statements, reporting relationships, delegations of authority, and position descriptions required to implement the new law.

The Center Management Team (formerly known as the Senior Management Team) collaborates on day-to-day management and policy decisions facing the Center, as well as long-range planning, budgeting, and policy development. In making its decisions, the team considers scientific, economic, international, and social issues and their impact on the Center. A project manager documents action items and decisions to ensure that these actions and decisions are implemented.[1]

Efforts to use science-based efficient risk management, to obtain maximum public protection with limited resources, continued during the year. These efforts included full and successful implementation of the Center's Activity-Based Costing program. This initiative emphasizes and supports the Center's "Back to Basics" approach to our strategic goals and allows us to bring increased discipline to our business practices. The successful deployment of the component program, Activity Time Reporting, allows us to better understand, manage, define, and assign the true costs of doing business.

We implemented new strategic human capital management activities, as part of our results-oriented management emphasis. For example, the CVM Staff College completed the development and delivery of New Reviewer Training for the current reviewers, as well as the new animal drug reviewers recently hired in the Office of New Animal Drug Evaluation (ONADE). The Staff College also delivered an ONADE Reviewer's Guide to reinforce the guidance received in the training. In addition, the CVM Staff College obtained full accreditation through the Maryland State Board of Veterinary Medical Examiners for the College's Scientific Seminar Series.

Appointments of individuals to serve in key positions are essential to the success of any organization. We made one such selection during the year, the appointment of Dr. Marleen Wekell as Acting Director of CVM's Office of Research.

[1]CVM's Center Management Team members are as follows:

Dr. Stephen F. Sundlof, Director, Center for Veterinary Medicine
Dr. Linda Tollefson, Deputy Director, Center for Veterinary Medicine (until September 15, 2005)
Dr. Andrew J. Beaulieu, Director, Office of Minor Use & Minor Species Animal Drug Development
Ms. Catherine Beck, Associate Director for Policy and Executive Programs
Dr. David Grau, Senior Management Consultant
Dr. William Flynn, Director, Policy and Regulations Staff
Dr. Daniel G. McChesney, Director, Office of Surveillance and Compliance
Mr. David E. Wardrop, Jr., Director, Office of Management
Dr. Marleen Wekell, Acting Director, Office of Research
Dr. Steven D. Vaughn, Director, Office of New Animal Drug Evaluation

We carried out our mission of protecting public and animal health in a variety of ways during FY 2005, including initiatives taken during times of national and regional disaster. For example, several CVM veterinarians joined Public Health Service colleagues in Baton Rouge to direct triage, treatment, and rehabilitation of companion animals evacuated from areas affected by Hurricane Katrina. Katrina caused an unexpected increase in disease in the Gulf Coast region's catfish industry, and the supply of a needed approved drug was short; CVM authorized Medically Necessary Veterinary Product status to another drug to treat the diseased catfish. The Center also provided advice on the use in animal feed of silt-covered grain from Pennsylvania fields flooded by rains from Hurricane Ivan.

The accomplishments of an organization are often reflected in the public recognition of its people. The Food and Drug Administration and CVM management during the year recognized the outstanding work of our Center employees through the presentation of a large number of group and individual awards. Of special note, Dr. Marilyn N. Martinez of ONADE won the 2005 FDA Honor Award, Excellence in Review Science. Full details for all the awards are in Appendix C.

Many other achievements by our employees deserve mention. For instance, the efforts of Dr. Mack Holt, Director of CVM's Office of Animal Care and Use, have been largely responsible for the fact that all FDA animal care and use facilities are now fully accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International (AAALAC, International). This includes accreditation of facilities in all five of FDA's centers, the National Center for Toxicological Research, and the Office of Regulatory Affairs. "Fully accredited" AAALAC status is the "gold standard" in laboratory animal care and use, symbolizing to the public and biomedical research communities that the program is operating at standards that epitomize quality animal care and use.

The large number of articles published by CVM scientists during the year attests to their professional productivity. The article topics ranged from antimicrobial resistance to drug metabolism and residues, biotechnology, and more. We have included a complete publications list in Appendix D.

In June and July 2005, CVM's Office of Research hosted two scientists from China's Institute of Veterinary Drug Control. The Institute is considering developing a microbial monitoring system similar to the NARMS program CVM helped establish in 1996. The Chinese scientists spent six weeks learning the various techniques employed by scientists in the Office's Division of Animal and Food Microbiology to identify bacteria recovered from animals and from meats derived from animals. Our scientists provided information on developing and using a database, designing a valid sampling plan, developing strategies to integrate laboratory and epidemiologic resources, and gaining public support for their programs.

It's been a busy, productive year – made possible by our staff of motivated, talented people. Their contributions cause our Center Management Team to be optimistic about the challenges of FY 2006 and beyond. We look forward to working with others in FDA, and our stakeholders and partners, as we face the tasks ahead of us.

We believe that the reader can best appreciate the Center's FY 2005 accomplishments by understanding what CVM is all about – our mission, plans, organization, sphere of influence, and so on. Thus, the first major section of our annual report is "About CVM."

Members of CVM's Center Management Team discuss key issues

Our Mission and Guiding Principles

OUR MISSION

The Center for Veterinary Medicine is a consumer protection organization. We foster public and animal health by approving safe and effective products for animals and by enforcing other applicable provisions of the Federal Food, Drug, and Cosmetic Act and other authorities.

OUR GUIDING PRINCIPLES

We are committed to:

Health Protection. We honor our role in protecting the health of people and animals, and value the principles and spirit of the supporting laws and regulations.

Integrity. We conduct ourselves with honesty and integrity, recognizing that upholding the public trust requires the highest standards of moral and ethical conduct.

Quality. We achieve excellence through the ongoing development of our competencies and continuous quality improvement in all our processes. In particular, we recognize the value and importance of science and law in reaching quality and timely regulatory decisions.

Teamwork. Everyone's contribution is important. Working together, we place the mission of the Center first and align our contributions, whether individual or in teams, toward that end. We conduct ourselves in accordance with the principles of consultative and participative decision-making.

Communication. We communicate information, ideas, decisions, and provide feedback, internally and external to the organization, in a candid, timely, constructive, and clear manner.

Equity. We treat our customers and each other with fairness, courtesy, respect, and compassion while fostering an atmosphere of mutual trust.

Diversity. We promote workforce diversity to strengthen and enrich the Center.

Innovation. We apply new concepts, ideas, and creative approaches to improve current operations and to meet the challenges of the future.

Safety and Health. We seek to ensure a safe and healthful workplace.

Quality of Worklife. We create and use programs that enhance our quality of worklife to improve our ability to carry out the mission of the organization.

Our Strategic Plan

CVM's strategic plan reflects the principles set forth in the President's Management Agenda, the 500-Day Plan initiative of the Secretary of Health and Human Services, and the Food and Drug Administration's Strategic Action Plan.

Our plan, "CVM's Back to Basics Approach for Carrying Out Our Public and Animal Health Mission," commits us to focus on our *core functions*:

- Animal drug review (pre-market activities)
- Compliance-related actions
- Post-approval monitoring
- Animal feed safety

To help us focus on the basics, our plan establishes the following goals. We will:

- set priorities (reviewed annually) and say "no" to lower priority items;
- improve, and bring discipline to and through, our business practices;
- support and use good science in establishing solid regulatory policy;
- improve the capacity of the organization to meet current and future demands on the Center; and
- develop revenue enhancing programs for core services.

Our Organization and Responsibilities

We carry out our mission through the efforts of people who are organized into six offices: the Office of the Director; the Office of MUMS Animal Drug Development; the Office of New Animal Drug Evaluation; the Office of Surveillance and Compliance; the Office of Research; and the Office of Management. All of our offices are located in Rockville, MD, except the Office of Research, whose facilities are located in Laurel, MD.

OFFICE OF THE DIRECTOR (OD)

The Office of the Director directs overall Center activities, coordinates and establishes Centerwide policy, and provides guidance for the implementation of the Center's "Back to Basics" strategic plan. The Center Director serves as CVM's representative and spokesperson concerning our activities, interacting with the general public, industry, the media, other government agencies, and national and international organizations.

The Director approves new animal drug applications, and exercises other statutory authority that has been delegated to him. Other functions are performed through a Deputy Director, an Associate Director for Policy and Executive Programs, and directors of the other offices within CVM. The Office of the Director coordinates the development of policy and regulations to guide industry and protect public and animal health, conducts communication and education programs, provides project management support for the Center, offers the services of the CVM Ombudsman, manages the Veterinary Medicine Advisory Committee, and coordinates international activities in the Center. The Office of Animal Care and Use coordinates accreditation and compliance with regulatory requirements by the Agency's animal care and use programs, and provides consultation on animal care and use issues.

OFFICE OF MINOR USE AND MINOR SPECIES (OMUMS) ANIMAL DRUG DEVELOPMENT

The Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act) provided for the establishment of OMUMS Animal Drug Development. The Office reports directly to the Director of the Center for Veterinary Medicine, and is responsible for overseeing the development and legal marketing of new animal drugs for minor uses in major species (disease conditions that are rare) and minor species such as small pet mammals, birds, reptiles, and zoo animals, as well as animals of agricultural importance such as fish, goats, pheasants, and bees.

Dr. Andrew Beaulieu, Director, and Dr. Meg Oeller of the Office of Minor Use and Minor Species Animal Drug Development

OMUMS Animal Drug Development is responsible for implementing the provisions of the MUMS Act relating to Designation and Indexing, and is assisting in the drafting of the implementing regulations for Conditional Approval. If a drug is "designated" under MUMS, it is granted seven years of marketing exclusivity, protecting it from generic copying and from approval of another pioneer application for the same drug, in the same dosage form, and for the same intended use. Indexing allows the legal marketing of certain unapproved drugs that have been reviewed by a qualified expert panel. Conditional approval allows a drug sponsor to make a drug available on the market before the company has collected all the necessary effectiveness data.

The Office is currently responsible for designating new animal drugs. This sometimes involves a determination of whether the intended use of a new animal drug qualifies as a minor use in a major species. Once implementing regulations are finalized, OMUMS will also be responsible for all aspects of animal drug Indexing.

OFFICE OF NEW ANIMAL DRUG EVALUATION (ONADE)

ONADE's mission is to protect the public health by ensuring the availability of safe and effective animal drugs to meet the therapeutic and production needs of animals. ONADE administers the core function of drug review – it directs the approval process for animal drugs. FDA must review an animal drug for safety, effectiveness, and quality before the drug can be legally marketed in interstate commerce. CVM approves drugs intended to benefit the health and productivity of food animals and the health of companion animals.

Dr. Bernadette Dunham, Deputy, and Dr. Steven Vaughn, Director, Office of New Animal Drug Evaluation

Drug sponsors must submit results of clinical tests to establish drug safety and effectiveness. Sponsors of drugs intended for food animals must also prove that food products derived from treated animals do not contain unsafe drug residues, and that the food products are safe with respect to microbial safety. The sponsors must develop analytical methods to detect and measure drug residues in edible animal products. The Food, Drug, and Cosmetic Act provides for approval of both pioneer and generic animal drugs, and for FDA-granted authority to

use investigational animal drugs. CVM classifies the animal drugs it approves, for distribution and use purposes, as over-the-counter, prescription, or Veterinary Feed Directive.

ONADE administers the Animal Drug User Fee Act of 2003, which authorizes FDA to collect fees in support of the review of new animal drugs.

OFFICE OF SURVEILLANCE AND COMPLIANCE (OS&C)

This Office has primary responsibility for three of CVM's core functions: compliance-related actions, post-approval monitoring, and animal feed safety. OS&C monitors the safety and effectiveness of approved drugs after they enter the market. This function includes assessing the significance of reported adverse reactions in treated animals, and working with sponsors to ensure that their marketed drug products remain safe and effective as labeled. Working with the U.S. Department of Agriculture and State agencies, OS&C monitors the occurrence of unsafe drug residues in meat and poultry products, and guides efforts to protect consumers through educational and enforcement activities related to drug residues. OS&C performs a similar function, working with FDA's Center for Food Safety and Applied Nutrition, with regard to domestic and imported aquacultured products. The Office coordinates enforcement actions against unapproved drugs that are on the market and that threaten public and animal health. Working with epidemiologists in the Office of Research, the OS&C utilizes epidemiological skills to protect public and animal health.

Dr. George Graber, Deputy, and Dr. Dan McChesney, Director, Office of Surveillance and Compliance

OS&C conducts surveillance and compliance programs to protect animal feed from contamination by toxic materials such as mycotoxins, pesticides, heavy metals, and industrial chemicals, and to prevent the establishment and amplification of bovine spongiform encephalopathy (BSE) through feed. The Office administers the feed mill licensing program, and coordinates biennial inspections of feed manufacturers. It approves food additives and reviews genetically modified plant varieties for animal feed safety. OS&C coordinates the Center's counterterrorism efforts. The Office's Bioresearch Monitoring staff oversees inspections of both nonclinical (laboratory) and clinical studies, to provide assurance of the integrity of data submitted in support of animal drug applications. OS&C also coordinates the Center's administrative actions involving approved drugs, such as actions to withdraw drug approvals.

OFFICE OF RESEARCH (OR)

This Office conducts applied research in support of regulatory decision-making related to each of CVM's core functions. OR operates from a state-of-the-art research complex containing offices, laboratories, animal buildings, and pastures.

In support of the drug review function, OR conducts studies in animal drug safety and efficacy, antimicrobial resistance mechanisms, metabolism, standardization of test methods, and pharmcokinetics/pharmacodynamics. The goal of these efforts is to provide a science base for guideline development. OR supports the illegal tissue residue compliance program of the Center through the development of analytical methods and evaluation of screening tests for detection of drug residues in imported and domestic food products. The Office is responsible for the post-approval

Dr. David Batson, Acting Deputy, Dr. Marleen Wekell, Acting Director, and Denise Strekal, Secretary, Office of Research

monitoring of retail meats for drug resistant foodborne pathogens under the National Antimicrobial Resistance Monitoring System, and molecular typing of those pathogens as part of the national PulseNet program. OR conducts research to understand the microbiology of animal feeds, and the dissemination of resistant organisms via livestock feeds. The Office is also developing methods to detect material, prohibited by the BSE feed regulation, that could compromise animal feed safety.

OR prepares a detailed annual report; for a copy, write to Center for Veterinary Medicine, Office of Research, 8401 Muirkirk Road, Laurel, MD 20708, attention Denise Strekal.

OFFICE OF MANAGEMENT (OM)

This Office has primary responsibility in four major program areas: budget and finance, management services, information resources management, and training/employee development. OM provides executive leadership and direction for the Center and Agency on management programs, policies, and issues.

OM leads and directs the planning, development, and execution of the CVM budget. This includes analysis, formulation, and presentation of budget issues. OM manages and provides leadership for the implementation and delivery of financial activities associated with the Center's user fee program. It also serves as the Center liaison with the Agency concerning Government Accountability Office and Inspector General studies/inquiries.

OM provides coordination and leadership for the Center's Activity-Based Costing/Activity Time Reporting System, and integrates it into the business culture of the Center's operation.

The CVM Staff College is located in OM where the staff directs the development and implementation of the competency-based management, leadership, team-building curriculum, and an extensive scientific/technical curriculum. The College sets the Center's expectations with regard to required competencies through the Staff College Knowledge Center.

OM serves as the focal point for management and directs administrative interaction with the CVM program offices and other FDA offices to assist with the efficient delivery of administrative services to the Center's employees. OM provides liaison services for activities that include space and workplace planning, facilities management and operations, and workplace safety. In addition, OM represents management on Center issues that involve the implementation of the FDA/NTEU[2] Collective Bargaining Agreement.

David Wardrop, Director, and Barbara Leach, Deputy, Office of Management; and Melissa Starinsky, Director, Staff College

[2] National Treasury Employees' Union

The Office provides the Center's liaison services to the Agency's Office of Shared Services, the Rockville Human Resources Center, and the Office of the Chief Information Officer to ensure efficient and effective administrative and information resources management services.

OM supports the vital information resources management function to enhance employees' abilities to efficiently work with the integrated Information Technology (IT) systems to reach CVM goals.

Our Sphere of Influence

CVM's efforts to help ensure that domestic and imported animal food products are safe affect millions of consumers. American consumers eat – on the average – 115 pounds of meat, 70 pounds of poultry, 15 pounds of fish, 585 pounds of dairy products, and 30 pounds of eggs each year. Besides protecting the health of consumers, CVM works to safeguard the health of food-producing animals in the United States: 95 million cattle, 60 million pigs, 9 billion chickens, 275 million turkeys, and 6 million sheep. The United States produces over $100 billion worth of livestock and livestock products each year.

CVM approvals are now in effect for several hundred animal drug applications, including generics, for use in food-producing animals. We have approved many of these drugs for administration through animal feed. CVM has licensed over 1,100 firms that manufacture medicated feeds, under a law passed by Congress in 1996. And we have published regulations that authorize use of more than 50 food (feed) additives.

Several hundred more approved animal drug applications, including generics, are available to maintain the health of our nation's growing pet population, which now number 65 million dogs and 75 million cats, in addition to 10 million birds and 6 million horses.

Altogether, we regulate activities of some 6,600 feed manufacturers and related firms, nearly 300 animal drug manufacturers and other sponsors of animal drug applications and Type A Medicated articles, many thousands of livestock and poultry producers, and firms in a variety of specialized industry groups. The drugs we approve help the nation's 73,000 veterinarians accomplish their task of maintaining the health of the nation's animals.

Our Stakeholders and Partners

OUR STAKEHOLDERS

Many organizations, and millions of individuals, have a stake in the outcome of CVM's work. They include consumers, animal owners, veterinarians, and firms in the regulated industries – companies that market the drugs, feeds, and other products that we regulate. Our stakeholders also include trade associations; consumer organizations; State, Federal, and foreign regulatory agencies; international standard-setting organizations; and Congress.

We use a variety of methods to keep stakeholders informed, and to seek their advice and opinions about our policies and programs. These methods include public meetings; requests for comment on proposed regulations and guidance documents; CVM UPDATES; the CVM website; and a variety of informal means such as letters, phone calls, and emails.

OUR PARTNERS

Our success in promoting and protecting the public health depends not only on the active involvement of our stakeholders, but also on the formation of partnerships with those whose goals align with ours. Government downsizing, a changing economy, technical advances, and other factors have prompted FDA and CVM increasingly to seek out partnering opportunities to maximize the use of our resources.

The concept of collaboration and partnership is generally known as leveraging, and we are working to make it one of the foundations of our day-to-day operations. Our partners include:

- Other Federal agencies with whom we share related regulatory responsibilities, such as the U.S. Department of Agriculture's (USDA) Food Safety and Inspection Service (e.g., surveillance for animal drug residue and antimicrobial resistance) and Animal and Plant Health Inspection Service (e.g., regulatory activities related to BSE), and the U.S. Environmental Protection Agency (EPA) (e.g., regulation of drugs that are also pesticides). For example, the Interagency Residue Control Group, with members from FDA, USDA, and EPA, coordinates information on residues of animal drugs, pesticides, and environmental contaminants in animal food products.
- Centers for Disease Control and Prevention, National Center for Infectious Diseases (e.g., surveillance for antimicrobial resistance and foodborne disease, and surveillance for variant Cruetzfeld-Jacob disease, avian influenza and other zoonotic diseases).
- USDA's Agricultural Research Service and Cooperative State Research, Education, and Extension Service.
- State agencies, which partner with us to conduct inspections for compliance with the BSE feed regulation and other feed inspections, and to carry out other regulatory and surveillance functions. We work very closely with the Association of American Feed Control Officials.
- Veterinarians, who share with us numerous public and animal health goals such as testing and surveillance of animal drugs for safety and effectiveness, avoiding drug residues in food products, minimizing the development of antimicrobial resistance through prudent drug use practices, and educating producers and related industries as to their public health responsibilities.
- Foreign regulatory agencies that have responsibility and authority for controlling animal drugs and feeds in their countries; we leverage such international work through our participation and leadership in the International Cooperation on Harmonisation of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH), Codex Committee on Residues of Veterinary Drugs in Food (CCRVDF), and other multilateral organizations.

We partner through cooperative agreements, cost-sharing contracts, cooperative research and development agreements (CRADAs), interagency agreements (IAGs), co-sponsorship agreements, and informal agreements. We hold joint workshops, co-sponsor training sessions, work with scientists on mission-related research, and cooperate with others in many ways.

We include a number of examples of current partnership arrangements in this annual report.

FISCAL YEAR 2005 CHALLENGES AND ACCOMPLISHMENTS

Introduction

Although we are organized into six separate offices, our Guiding Principles call for the staff of the Center for Veterinary Medicine to work together, placing the mission of the Center first. In fact, most of our significant accomplishments involve the efforts of people from two or more offices, through teams, committees, and day-to-day coordination.

Thus, we organize our presentation of FY 2005 accomplishments not according to office structure, but according to crosscutting topics. These topics reflect issues of significant public interest. We introduce each of these areas of concern with a statement of the challenges that we face as we attempt to meet our "Back to Basics" goals.

To help us achieve our strategic goals in FY 2005, we established targets for the year – a number of specific *performance goals* (the performance goals may be either program goals or management goals). Individual offices have primary responsibility for achieving some of the performance goals, but two or more offices share many of the performance goals because the goals relate to activities that require collaborative efforts.

We highlight our performance goals below, in the appropriate sections, and indicate (with a or) whether we accomplished the goals.

We have worked during the past year to focus on the priorities in the President's Management Agenda and the HHS-wide program and management objectives. We also focused on the priorities stated in FDA's Strategic Action Plan: efficient risk management, better-informed consumers, improved patient and consumer safety, protection from terrorism, and more effective regulation through a stronger workforce. We have indicated below some examples of how our FY 2005 accomplishments responded to the Agency's priorities.

Because this annual report celebrates a century of food and drug regulation, we have – as appropriate – included lists of regulatory milestones related to individual topical areas.

Increasing the Availability of Safe and Effective Animal Drugs

Milestones in Animal Drug Approval Legislation

1938 ..... *Food, Drug, and Cosmetic Act provided authority for approval of drugs, based on safety, prior to marketing. Among the early animal drug approvals were Spohn's Udder Aid (which contained oxyquinoline benzoate, lanolin, and camphor), Neo-Polycin Ophthalmic (which contained neomycin, bacitracin, and polymixin), and Glover's Imperial Dog Capsules (n-Butyl chloride). The oldest currently active approval is for Sulfodene Medication for Dogs, approved in April 1943.*

1962 ..... *Drug Amendments provided for preclearance based on effectiveness, and an efficacy review for drugs approved before 1962.*

1968 ..... *Animal Drug Amendments consolidated separate approval provisions for animal drugs (drug, food additive, and medicated feed). This change eliminated the cumbersome process that required three separate approvals for drugs administered through feed, and established a separate approval process for medicated feeds.*

1988 ..... *Generic Animal Drug and Patent Term Restoration Act provided for approval of generic drugs, and patent term restoration for original approvals.*

1996 ..... *Animal Drug Availability Act passed to improve availability of approved animal drugs by changing the effectiveness standards and altering the administrative approval processes.*

2003 ..... *Animal Drug User Fee Act provided authority to collect user fees from sponsors, to enable FDA to accelerate and improve the animal drug review process.*

2004 ..... *Minor Use and Minor Species Animal Health Act to provide incentives for submitting applications for drugs for minor species or for limited uses.*

FY 2005 Performance Goals

Continue implementation of the Animal Drug User Fee Act of 2003 (ADUFA).

*Meeting this goal accomplishes the FDA strategic goal of **Improving the Quality of Health Care**.*

Continue to develop and validate multi-residue drug screening methods (for chemical and microbiological hazards), and continue to conduct method validation studies for the approval of applications for new drugs for food-producing animals.

THE CHALLENGE

Statutory standards and the needs of our stakeholders – and especially the needs of the billions of animals whose health we seek to protect – require that we make the right preapproval decisions, and do so efficiently and expeditiously. CVM's challenge is to protect the public health by assuring that there is an adequate supply of animal drugs to meet therapeutic and production needs. The Animal Drug User Fee Act of 2003 challenges CVM to expedite and improve the review of new animal drug applications so as to increase the availability and diversity of safe and effective drugs.

FY 2005 ACCOMPLISHMENTS

We responded to the preapproval challenges in a number of ways, as described below. In general, we directed these actions toward achieving the FDA strategic priority of improving the quality of health care, focusing our efforts on the Agency's priority of increased productivity in new drug development. These efforts included initiatives directed toward the strategic plan's objective of providing a timely, high-quality, and cost-effective process for review of pre-market submissions.

ANIMAL DRUG USER FEE ACT OF 2003 (ADUFA)

The Law

Implementing ADUFA was a major CVM emphasis during FY 2005. ADUFA authorizes FDA to collect fees in support of the review of new animal drugs. The legislation authorizes the collection of fees totaling $43 million over five years, to enable FDA to hire and train additional scientific reviewers and implement enhanced processes to accelerate and improve the review process.

The Benefits

This legislation is helping FDA expedite and improve its review of applications for new animal drugs so that safe and effective new products will be available more quickly. Specifically, the law establishes performance goals including five-year goals to be implemented by the end of FY 2008. This includes reviewing and acting on 90% of:

- new animal drug applications (NADAs) and reactivations of such applications within 180 days after submission date;
- nonmanufacturing supplemental animal drug applications (i.e., supplemental applications for which safety and effectiveness data are required) and reactivations of such applications within 180 days after submission date;
- manufacturing supplemental animal drug applications and reactivations of such applications within 120 days after submission date;
- investigational animal drug study submissions within 180 days after submission date;
- investigational animal drug submissions consisting of protocols that the Agency and the sponsor consider to be an essential part of the basis for making the decision to approve or not approve an animal drug application or supplemental animal drug application, without substantial data within 50 days after submission date; and
- administrative animal drug applications (NADAs submitted after all scientific decisions have been made in the investigational animal drug process, i.e., prior to the submission of the NADA) within 60 days after the submission date.

We anticipate that ADUFA will bring substantial savings to the animal drug industry in regulatory review and developmental expenses. A faster, more predictable review process is expected to spur more research and development by the animal drug industry. The law also requires the Agency to adopt administrative processes to ensure that review times for generic animal drugs (abbreviated new animal drug applications, or ANADAs) do not increase from their pre-ADUFA levels due to activities under ADUFA.

Implementation

The law requires the Agency to meet annual performance goals. We met the performance goals for FY 2004, the first year of implementation. The following summarizes accomplishments and status as of the end of FY 2004:

- ADUFA Performance. FDA met or exceeded all the review timeframes defined under ADUFA for FY 2004 for applications and submissions that have been acted on as of September 30, 2004. Additional applications and submissions received in FY 2004 were pending review and action, but are still within ADUFA time frames. FY 2004 performance will be updated in FY 2005 to reflect these pending actions.
- FDA Backlog. The 833 submissions not associated with ANADAs that were pending before September 30, 2003, have been reviewed and acted upon. FDA was required to review and act on pending NADAs, supplemental NADAs, and investigational new animal drug submissions (INADs) within 24 months after user fee payments were initiated.
- FDA Hiring. FDA has made substantial progress in recruiting for its review staff and will meet its goal of having 50 percent of additional FDA review staff recruited and on-board by the first quarter of FY 2006.
- Guidance Development. On March 15, 2004, the Agency published Guidance for Industry #170, *Animal Drug User Fees and Fee Waivers and Reductions*, to help industry understand the ADUFA fee structure and the options available to individuals who qualify for a fee waiver or reduction. On September 28, 2004, the Agency published Guidance for Industry #173, *Animal Drug Sponsor Fees under the Animal Drug User Fee Act (Draft Guidance)*.

The FY 2004 ADUFA Financial Report shows that we met the legal conditions that must be satisfied before the Agency can collect and spend user fees.

During FY 2005, we worked to achieve goals set for the year. Performance and financial reports for FY 2005 will be published separately.

ACTIONS TO INCREASE THE EFFICIENCY OF THE REVIEW PROCESS AND ENSURE THE SAFETY AND EFFECTIVENESS OF ANIMAL DRUGS

The Center's Office of New Animal Drug Evaluation (ONADE) uses a Balanced Scorecard to evaluate its performance. The scorecard has four attributes consisting of:

Productivity. We continue to surpass our productivity measurements by exceeding all ADUFA goals for FY 2004. We are implementing a quality systems approach as our Tactical/Operational Plan for the Office.

Quality. During FY 2005, we substantially expanded the Quality Assurance (QA) Team within ONADE. This expansion enabled ONADE to update all of our process maps, i.e., visual representations of our processes; this helps us identify needed SOPs. One member of our QA team is facilitating the implementation of the quality system for the Office. We continue to write SOPs and guidances to define our work procedures and products as well as to communicate to the regulated industry our expectations for incoming submissions.

Employee Satisfaction. We rely in part on the Agency's Quality of Work Life Annual Survey and the Center's 360 Degree Feedback assessment. We also rely on the coaching and advice from the Office Director's Executive Coach

and the Center's Senior Program Management Specialist to guide our decision-making and approaches to improve the quality of our employees' worklife. This year, we added the results of the Gallup Q12 poll to our sources of feedback information. Each organizational unit within ONADE held follow-up discussions to identify further opportunities to increase employee satisfaction. In addition, working with the CVM Staff College, we provided multiple course curricula including a new reviewer orientation course for ONADE reviewers.

Customer Satisfaction. Following discussions with the Animal Health Institute (AHI), CVM received from AHI the results of a customer satisfaction survey and is analyzing the results. CVM intends to engage other stakeholders to expand the source of feedback information it receives. We began meeting on a regular basis with the Animal Drug Alliance to address issues and concerns from the generic animal drug sponsors. All of this is part of the High Performance Organization model employed by CVM.

In addition, we developed guidance to expedite the approval process including revision and republication of a new toxicology section for Guidance for Industry (GFI) #3, *General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals*. We also published for comment draft GFI #123, *Development of Target Animal Safety and Effectiveness Data to Support Approval of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for Use in Animals*. This draft guidance provides recommended approaches for drug sponsors on the development of target animal safety and effectiveness data to support approval of veterinary NSAIDs that reduce the production of prostaglandins by inhibiting the cyclooxygenase (COX) pathway.

RESEARCH TO SUPPORT ANIMAL DRUG REVIEW

Drug sponsors are responsible for submitting studies to prove their drugs are safe and effective. Complementary work – accomplished by CVM, its contractors and collaborators – may alter the type and number of studies required for approvals, thus improving the efficiency of the drug approval process. An example of this is a pharmacokinetics/pharmacodynamics program to assess the effects of drugs in diseased animals, an important contribution because most data submitted to CVM are generated in healthy animals.

One of the steer calves to be used in CVM's Office of Research pharmacokinetic data study

Initial analysis of pharmacokinetic data from the study of enrofloxacin in beef steers indicates that in the presence of respiratory disease, blood levels of the drug are increased, but less active drug reaches the site of infection (an effect that may be different depending on the drug's route of administration). Also, there was no change in the susceptibility to enrofloxacin or ciprofloxacin, indicating that no resistance appeared to be developing within the two- to four-week timeframe of the experiments. Additional studies will be conducted in this program to improve the Center's ability to determine whether predictions may be biased when based upon information obtained from normal healthy animals.

We have completed the animal phase of a similar pilot study with tilmicosin (a macrolide antibiotic) in beef steers. We measured drug levels in the plasma and at the site of infection (bronchial fluid), and we are currently analyzing the results.

Increasing Drug Availability for Aquaculture and Other Minor Uses/Minor Species

MUMS Milestones

1982 ..... *USDA and FDA established a national program for approval of minor use animal drugs, under the USDA's Interregional Project Number 4 (IR-4).*

1983 ..... *FDA issued regulation 21 C.F.R. § 514.1(d), which defined "minor use" and specified data for minor use drugs that would meet statutory standards.*

1993 ..... *USDA established National Research Support Project #7 (NRSP-7) to obtain approvals of minor use drugs.*

1996 ..... *The Animal Drug Availability Act contained a provision for study to determine the need for legislation related to minor use drugs.*

2004 ..... *Congress passed the Minor Use and Minor Species Animal Health Act to encourage the development of drugs for these uses.*

THE CHALLENGE

The Minor Use and Minor Species Animal Health Act of 2004 (MUMS Act) challenges CVM to implement measures that will significantly expand the availability of drugs for minor uses and minor species. Because the potential sales volume is low, animal drug manufacturers lack economic incentive to seek animal drug approvals for minor uses (diseases that are rare) or minor species (animal species other than cattle, horses, pigs, chickens, turkeys, dogs, or cats). The need in aquaculture is a good example. The U.S. aquaculture industry is expanding, and the need for therapeutic and production drugs is growing as well.

FY 2005 Performance Goals

Implement the MUMS legislation by processing requests for designation for specific minor use and minor species for new animal drugs and prepare proposed and final regulations to implement the MUMS Act according to the schedule described in the law.

*Meeting this goal accomplishes the FDA strategic goal of **Improving the Quality of Health Care**.*

IMPLEMENTATION OF MUMS LEGISLATION

The Law and Its Benefits

This legislation provides innovative, flexible ways to provide drugs to treat minor animal species as well as uncommon diseases in the major animal species. It is designed to help pharmaceutical companies overcome the financial roadblocks they face in providing limited-demand animal drugs. The new law is expected to benefit certain agricultural groups, people who own small or unusual pets, and zoo veterinarians. The new law modifies provisions of the Federal Food, Drug, and Cosmetic Act in three key ways, providing for:

Conditional Approval. The sponsor of a minor use/minor species veterinary drug can ask CVM for "conditional approval," which allows the sponsor to market the drug after proving the drug is safe and establishing a reasonable expectation of effectiveness, but before collecting all of the effectiveness data needed to support a full approval. The drug sponsor can keep the product on the market for up to five years, through annual renewals, while gathering the required effectiveness data.

Indexing. Once implementing regulations are finalized, FDA may add a minor species drug to an index of unapproved new animal drugs that may be legally marketed when the potential market for the drug is too small to support the costs of the drug approval process, even under a conditional approval. This provision will be especially helpful to veterinarians treating zoo or endangered animals, and owners of minor pet species such as ornamental fish or caged reptiles, birds, or mammals.

Designation. This aspect of the legislation provides incentives for minor use/minor species approvals, such as grants to support safety and effectiveness testing. Sponsors must apply for designation prior to filing a new animal drug application for FDA approval. At the time that a designated drug gains approval or conditional approval, it is awarded seven years of exclusive marketing rights, which means that FDA will not approve another application for the same drug in the same dosage form for the same intended use until after the seven years have elapsed. This is two to four years longer than the protection provided from generic copying of nondesignated drugs. The MUMS marketing exclusivity also protects against approval of another pioneer (nongeneric) application for the same drug, in the same dosage form, for the same intended use.

Implementation

During FY 2005, we completed the process of establishing the statutorily mandated Office of MUMS Animal Drug Development, which involved establishing functional statements, reporting relationships, delegations of authority, and position descriptions. We are working on the development of internal office policies and procedures. Analysis of potential resource needs and basic IT system design with respect to such issues as document management and submission tracking is underway.

We proposed a regulation for implementing the "Designation" section of the MUMS Act during FY 2005. The proposed rule provides the functional requirements for drug sponsors that request MUMS designation for proposed new animal drugs. The rule also describes "exclusive marketing rights," which is one of the primary incentives for MUMS designation.

During the year, we processed over 50 designation requests (using interim processes) and granted our first designations under new section 573 of the statute. The designations were for Florfenicol (Aquaflor®), for use in controlling

diseases in four aquaculture species – catfish, hybrid striped bass, salmonids, and tilapia. Designations that are granted are posted on a list on the Minor Use and Minor Species page of the CVM website.

To the extent that the administrative procedures permit, the MUMS office has reached out to stakeholders to update them on the status of MUMS Act implementation. We have met with pharmaceutical companies to address questions about designation and conditional approval with regard to their products, and we have given general presentations about MUMS to a number of groups. We have also answered numerous telephone and email inquiries about various aspects of the MUMS legislation and its implementation.

RESEARCH TO SUPPORT DRUG APPROVALS

Antimicrobial Susceptibility Testing

During FY 2005, we conducted an international multi-laboratory trial using broth dilution to develop a standard for antimicrobial susceptibility testing (AST) of aquatic bacteria. This work resulted in two publications; in addition, we provided data related to a proposed guideline for disk diffusion AST of specified aquatic bacteria, an essential step in making this AST method an official method. These standards will be used internationally, allowing for valid comparisons between testing laboratories. The data derived from tests using this method will facilitate the appropriate treatment of fish diseases and will help regulatory agencies monitor for changes in antimicrobial susceptibilities of bacteria found in the environment.

Microbial research at CVM's Office of Research

Food Safety Database

As part of CVM's commitment to streamline the drug approval process for minor species, we developed a database of literature (designated the PhishPharm Database) detailing drug metabolism, residues, and pharmacokinetics in multiple fish species. This is a searchable database that provides information on the half-lives of drugs in fish, and serves as a tool for researchers and regulators. In FY 2005, we enhanced the database to include over 400 articles. The database will also be published on-line in FY 2006.

Analytical Methods

In order to ensure human food safety, drug sponsors are required to provide analytical methods to monitor for residues of sponsored drugs in food products from treated animals. Before a method can be developed, scientists must identify a suitable marker compound (parent drug or metabolite) to be used for monitoring. This step typically requires complex and expensive metabolism studies, which often are too difficult for minor species drug sponsors. In response, CVM scientists are generating data that can be used for developing methods for therapeutically important classes of drugs in farm-raised fish.

In the first of several planned studies, CVM scientists have studied the metabolism of albendazole, an important anthelmintic, in rainbow trout, tilapia, Atlantic salmon, and channel catfish. We have found that the first three species have similar metabolite profiles. However, studies completed during FY 2005 established that channel catfish have a somewhat different set of metabolites and a very different rate of metabolism. These studies have identified metabolites that can serve as marker residues of drug use and for which monitoring methods can now be developed.

We also completed during FY 2005 a study of the metabolism and residue depletion of ivermectin in rainbow trout. We found that approximately half of the parent drug is converted to an unknown metabolite; after identification, the metabolite may serve as the marker residue in fish.

Drug Residues in Seafood

During FY 2005, we continued to make progress in improving the efficiency of drug residue testing in aquatic species, including the development of multi-residue methods for screening/confirmation and quantification of drug residues for use both in preapproval and enforcement settings. This included:

Multi-residue procedures for screening/confirmation in salmon and other finfish. Using a published pesticide extraction technique, we developed during the fiscal year a method that is able to screen for about three dozen drug compounds in salmon. The method has been validated for use in salmon and trout and is currently being evaluated for use in tilapia and catfish. Because the method includes most drugs known to be approved outside the United States for use in finfish, it has the potential to be used in support of approvals under the MUMS legislation through use in the development of regulatory analytical methods.

Multi-residue procedures for quantitative analysis in shrimp. Procedures for quantifying residue do not exist for many of the drugs detected through the screening/confirmation procedure that our Office of Research has developed for shrimp. In FY 2005, we explored simple extraction techniques that could reliably and completely isolate these compounds from shrimp, so that they could be quantified. We evaluated and optimized a triple quadrupole mass spectrometer, which we found to be more suitable for measuring the quantity of a drug than the mass spectrometer that is used for the screening and confirmation testing.

Aquaculture research at CVM's Office of Research

Procedures for nitrofuran residues in channel catfish. In FY 2005, our Office of Research collaborated with the Gulf Coast Seafood Laboratory in FDA's Center for Food Safety and Applied Nutrition on a study to investigate the metabolism and depletion of nitrofurans in channel catfish. The study focused on the depletion of all four nitrofuran drugs commonly used in catfish.

Drug Residues in Honey

Honey is different than most food products that may contain animal drug residues. Seafood, meat, and milk contain large amounts of protein and fats, while honey contains primarily sugars. Because of these significant differences, the traditional approaches used to isolate drug residues do not work for honey. During FY 2005, we made progress in the development of a multi-residue procedure in honey, as we explored a variety of novel techniques and identified several promising approaches to the isolation of drugs from honey. We also conducted a study, with the cooperation of the U.S. Department of Agriculture's Bee Laboratory, in which we found that nitrofuran metabolites are the preferred markers for detecting nitrofuran usage in honeybees.

National Research Support Project #7 (NRSP-7).....

NRSP-7 is a national agricultural research program sponsored by the U.S. Department of Agriculture, in collaboration with CVM and others, to obtain clearances for drugs for minor species and minor uses. The program had a very active year during FY 2005. Its Public Master File (PMF) established in CVM for the use of oxytetracycline immersion for otolith marking of finfish has now been used by three different sponsors to support new animal drug applications that were approved. We announced in the *Federal Register* the availability of a complete PMF for the use of tylosin soluble powder for the treatment of American foulbrood in honeybees. Significant studies were submitted and/or accepted to support projects for the use of a progesterone intravaginal device for sheep, erythromycin for salmonids, and florfenicol for sheep.

At fiscal year end, NRSP-7 had 15 active projects, for rabbits, various fish species, sheep, goats, game birds, shrimp, and honeybees. To date, NRSP-7 files have supported 25 unique minor species drug approvals, and PMFs are available to support additional approvals.

Reducing Risk From Antimicrobial Resistance

Antimicrobial Resistance Milestones

1940s ..... *Beginning of use of antibiotics to treat disease in food-producing animals.*

1950s ..... *Introduction of antibiotics for use in feed of livestock and poultry.*

1969 ..... *Swann Committee report (UK) recommended certain restrictions in use of antibiotics in animals.*

1973 ..... *FDA issued a regulation, 21 C.F.R. § 558.15, requiring the submission of data and information related to antibiotic resistance developing as a result of use of antimicrobials in food-producing animals.*

1980s ..... *Two National Academy of Sciences studies found indirect but equivocal evidence that subtherapeutic use of antibiotics in animal feed caused a human health hazard.*

1993 ..... *CVM announced policy of restricting new antimicrobials for therapeutic use to a veterinarian's supervision.*

1998 ..... *CVM issued* A Proposed Framework for Evaluating and Assessing the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food-Producing Animals.

2004 ..... *CVM adopted guideline Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbial Effects on Bacteria of Human Health Concern (GFI # 152), which provides a risk-based process for assessing the resistance-developing potential of antimicrobial drugs.*

FY 2005 Performance Goals

- Continue to review previously approved new animal antimicrobial drug submissions with respect to antimicrobial resistance and human food safety and continue research to identify resistant organisms that lead to treatment failures.

*Meeting this goal accomplishes the FDA strategic goal of **Improving Health Outcomes**.*

- Continue the coordination of NARMS activities among FDA, USDA and CDC to result in the most unbiased presentation of timely, accurate data in the best interest of the public health.

*Meeting this goal accomplishes the FDA strategic goal of **Improving Health Outcomes**.*

- *Support for advanced World Health Organization training courses on the surveillance of* Salmonella *and antimicrobial resistance in foodborne pathogens.*
- *Publish in the Federal Register the draft Virginiamycin Risk Assessment for comment. As appropriate, incorporate comments received and finalize risk assessment.*

THE CHALLENGE

Scientific evidence demonstrates that the use of antimicrobial drugs in food-producing animals can result in the selection for resistant bacteria. Resistant foodborne bacteria can then be transferred to humans, resulting in illness. If the consumer needs antimicrobial drug treatment, that therapy may be compromised because the drugs of choice may be ineffective. CVM is challenged to develop policies and programs that reduce this risk to human health.

FY 2005 ACCOMPLISHMENTS

In cooperation with other agencies, CVM has undertaken proactive risk assessment and risk management, surveillance, research, and education programs to reduce the risk to human health that can result from the use of antimicrobials in food-producing animals. We achieved significant progress in these efforts during the past year, responding to the FDA strategic goal of improving health outcomes, and to the Agency Strategic Plan priority of reducing the major public health threat caused by foodborne illness.

ASSESSING RISK AND TAKING APPROPRIATE RISK MANAGEMENT ACTION

Virginiamycin Risk Assessment

In November 2004, FDA published a notice of availability and opportunity to comment on the *Draft Risk Assessment of Streptogramin Resistance in Enterococcus faecium Attributable to the Use of Streptogramins in Animals*. The risk assessment centered on the animal drug virginiamycin, which has been used for 30 years to promote growth and prevent or control disease in chickens, turkeys, swine, and cattle. CVM decided that it would conduct the risk assessment shortly after FDA approved Synercid in 1999 for treating vancomycin-resistant *E. faecium* infections in hospitalized humans. As many as 70,000 hospitalized patients in the United States may acquire a vancomycin-resistant *E. faecium* infection each year.

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

We have reviewed and categorized the comments on the risk assessment – received from a broad range of interested stakeholders, including representatives of consumer groups, the animal drug industry, veterinarians, and infectious disease physicians.

On the basis of this review, the Center has concluded that the draft risk assessment will not be revised at this time. However, the risk assessment will be revisited if new data become available that address the assumptions made in the Draft Risk Assessment, address the identified data gaps (e.g., the molecular genetics of streptogramin resistance

in enterococci), or indicate a change in the usage patterns of Synercid. In the meantime, we will continue to monitor the scientific literature, the results of surveillance studies, usage patterns of Synercid and other streptogramins, and other relevant data.

Continuation of Penicillin and Tetracycline Review .....

Our Office of New Animal Drug Evaluation (ONADE) staff continues to review previously approved new animal drug applications (NADAs) for penicillin and tetracycline with respect to antimicrobial resistance and human food safety. The Office has completed its review of approved NADAs providing for the use of penicillin for non-therapeutic uses. CVM management established a working group during the fiscal year to review the scientific basis for the 1977 notice of opportunity for hearing (NOOH) for penicillin products and to determine what route should be followed in order to bring penicillin production drug claims into line with current risk management policy. ONADE continues to evaluate the approved NADAs that provide for production uses of the tetracyclines to determine soundness and relevance of their human food safety determinations.

Commissioner's Decision on Withdrawal of Enrofloxacin for Use in Poultry.....

On July 24, 2005, the Commissioner of Food and Drugs signed his final decision withdrawing the approval of the new animal drug application for Baytril® (enrofloxacin) for treating bacterial infections in poultry. (This ruling does not affect other approved uses of the drug.) The Commissioner concluded that enrofloxacin has not been shown to be safe for use in poultry, and ordered withdrawal of the approval effective September 12, 2005.

This animal drug belongs to a class of drugs known as fluoroquinolones, a number of which are used in human medicine. CVM began proceedings to withdraw the poultry drug approval because of scientific data that showed that the use of enrofloxacin in poultry caused resistance to emerge in *Campylobacter*, a bacterium that causes foodborne illness. Chickens and turkeys normally harbor *Campylobacter* in their digestive tracts without causing poultry to become ill. Enrofloxacin does not completely eliminate *Campylobacter* from the birds' intestinal tracts, and those *Campylobacter* bacteria that survive are resistant to fluoroquinolone drugs. These resistant bacteria multiply in the digestive tracts of poultry; spread through transportation and slaughter; and are found on chicken carcasses in slaughter plants and retail poultry meats.

MONITORING FOR THE DEVELOPMENT OF RESISTANCE

Federal/State Monitoring Program.....

The expansion of the National Antimicrobial Resistance Monitoring System (NARMS) continued in 2005. The Center has also progressed in the development of a uniform website and reporting scheme for all three components of NARMS: the human isolates, slaughter plant isolates, and retail meat. The website is on line at http://www.fda.gov.cvm/coversheet2003.htm. The 2003 annual report went on line during FY 2005, and the 2004 report will soon be added.

The Center in June 2005 held an external review meeting focusing on all three components of NARMS. The three sponsoring agencies – CDC, USDA, and FDA – presented factual background information on NARMS to a seven-person outside expert panel and then asked specific questions of each member. The expert panel consisted of individuals with recognized expertise in the areas of public health surveillance of antimicrobial resistance, food safety epidemiology, antimicrobial susceptibility testing, and laboratory research in antimicrobial resistance. The Center plans to use the information from the external review to evaluate and enhance NARMS. We also plan to take the results from the expert review, plus the results from a review by the FDA Science Board, to a public meeting in FY 2006.

NARMS is a valuable resource that is revealing important trends in antimicrobial resistance to a wide variety of antimicrobial agents of importance to human and veterinary medicine. The NARMS-generated information is helpful in identifying the source and magnitude of antimicrobial resistance, and is important for the development of public health recommendations for the use of antimicrobial drugs in humans and food animals. NARMS has matured since its inception in 1996 and the Center determined that it could benefit from the input of experts on its key elements and future directions.

International Expansion of NARMS: Mexican Resistance Surveillance

The year 2005 marked a one-year extension of the ResistVet program in four agricultural states in Mexico. ResistVet is a surveillance system designed to identify outbreaks of foodborne illness, especially those that are multi-drug resistant, in time to respond with interventions to stop the spread of resistant pathogens. Several papers on the program have been published or are currently in development. The Mexican Ministry of Health has been very complimentary of the monitoring program and has agreed to continue support.

INTERNATIONAL TRAINING IN FOODBORNE ILLNESS CONTROL

Global Salm-Surv (GSS) is a worldwide network of laboratories and individuals involved in surveillance, isolation, identification, and antimicrobial susceptibility testing of foodborne pathogens. It is part of an effort by the World Health Organization (WHO) to strengthen the capacities of its Member States in the surveillance and control of major foodborne diseases, and to contribute to the global effort of containment of antimicrobial resistance in foodborne pathogens.

To help meet these goals, CVM provides financial support and personnel with expertise in the epidemiology and microbiology of foodborne disease. In FY 2005, WHO-GSS organized regional training courses in Cameroon, China, Mexico, Trinidad, and Russia, with additional courses planned for the fall of 2005 in Brazil, China, and Cameroon. Laboratory training is conducted for the isolation, identification, and antimicrobial susceptibility testing of *Salmonella* and other foodborne pathogens relevant to a region, such as *Escherichia coli, Salmonella typhi*, and *Vibrio cholerae*. The epidemiology curriculum was further improved with new learning objectives for epidemiologic training for foodborne disease outbreak detection and response.

CVM microbiologists (Drs. Shaohua Zhoa and Patrick McDermott) and an epidemiologist (Dr. Tom Chiller) participated as program developers and trainers, and as members of the Steering Committee. Regional strategies and action plans were developed at the WHO Strategic Meeting for the Global Salm-Surv Regional Centers and Training Sites in Copenhagen, Denmark, in April 2005. Also, closer collaboration with the U.S. PulseNet program was established to better respond to foodborne disease outbreaks.

PUBLIC HEALTH ACTION PLAN TO MITIGATE AND CONTAIN ANTIMICROBIAL RESISTANCE

A Federal Inter-Agency Task Force co-chaired by representatives of the Centers for Disease Control and Prevention, National Institutes of Health, and FDA (including CVM) made progress during the year in carrying out an action plan to address antimicrobial resistance issues. The Task Force presented an update of its priority action items and received comment at a public meeting held in June 2005 in conjunction with the annual meeting of the National Foundation for Infectious Diseases. The Task Force, which consists of representatives of a number of Federal health-related agencies, is currently working on a gap analysis to determine which action items have been completed and what still needs to be done.

The action plan, originally published in 2001, provides a blueprint for specific, coordinated Federal action to address the emerging domestic threat of antimicrobial resistance. Annual reports of progress in 2003, 2004, and 2005 are at http://www.cdc.gov/drugresistance/actionplan/aractionplan.pdf.

RESEARCH TO SUPPORT ANTIMICROBIAL RESISTANCE SURVEILLANCE AND REGULATION

Antimicrobial research at CVM's Office of Research

The overarching goal of antimicrobial resistance research at CVM is to identify and implement methods to reduce microbial hazards associated with antimicrobial drug use in food-producing animals. This includes basic and applied research focusing on the prevalence, propagation, and persistence of antimicrobial resistant bacteria in the animal production environment and on foods of animal origin. A comprehensive research effort will help ensure that any regulatory actions taken to control antimicrobial resistance will be based on sound science. Our FY 2005 research included several broad objectives, as follows.

Obtain information that has the potential to reduce the transfer of resistant animal pathogens to humans. Multi-drug resistant *Salmonella* serotypes other than Typhimurium and Newport have emerged in animals and humans in the United States. During FY 2005, OR scientists continued to use pulsed-field gel electrophoresis (PFGE)[3] to characterize a collection of *Salmonella* isolates (recovered from animals, retail meats, and ill humans) with regard to antimicrobial resistance phenotypes as well as genetic relatedness. This research has removed any doubts that humans can become infected and ill from bacteria carried by food-animal species and, if those bacteria have acquired resistance to antimicrobial agents, that resistance can be found in the human isolates.

Our accomplishments in this area are possible because of CVM's association with the PulseNet program, a national molecular subtyping (genotypic) network for foodborne disease surveillance. Our FY 2005 PulseNet-related accomplishments included subtyping of more than 1,000 *Salmonella*, *E. coli*, and *Campylobacter* isolates recovered from food animals, retail meats, and humans. We have identified multi-drug resistant (MDR) *Salmonella* serotypes and clones. At the end of the fiscal year, the CVM PulseNet database had more than 4,000 data entries. The data will allow CDC and CVM to monitor the emergence of MDR foodborne pathogens in the United States; to understand how bacterial antimicrobial resistance develops, disseminates, and persists in the animal production environment and in retail foods; and to understand how such pathogens infect humans.

Use existing microbiological collections to examine historical susceptibility of foodborne bacterial pathogens to antimicrobial agents. To better interpret the public health threat represented by current antimicrobial resistance levels, CVM contracted with the American Type Culture Collection (ATCC) to measure resistance among banked historical collections of *Salmonella*, *Campylobacter*, and *E. coli*. We have completed antimicrobial susceptibility testing of these isolates, and we plan studies to examine the genetic bases of resistance. Data from this study will help us better assess the impact over the past six decades of antimicrobial use in veterinary and human medicine.

[3] Scientists use PFGE to separate especially long strands of DNA by length, to differentiate between samples. PFGE is used for gene mapping, medical epidemiology, and other purposes.

Identify the food-producing animal species that contribute to antimicrobial resistance in foodborne pathogens. CVM's ongoing Bacterial Source Tracking project investigates the animal origin of human *Salmonella* and *Campylobacter* infections. OR scientists are using a variety of techniques to determine with some level of certainty if a human *Salmonella* infection can be traced to a specific food-producing animal species. Results obtained during FY 2005 show that, while serotyping, antibiograms, multilocus sequence typing, and PFGE can show some host-specific clustering, it will require a combination of phenotypic and genotypic methods to identify the animal source of a human infection. This requires further research, which we plan to conduct.

Controlling Risk From Bovine Spongiform Encephalopathy (BSE)

BSE Milestones

1986 ..... *BSE is diagnosed in cattle in the UK.*

1996 ..... *Variant Cruetzfeldt-Jakob Disease (vCJD) is diagnosed in humans in the UK, and is epidemiologically linked to BSE.*

1997 ..... *FDA adopted BSE feed rule.*

2003 ..... *First BSE-infected cow is discovered in the United States.*

2004 ..... *FDA and USDA issued advanced notice of proposed rulemaking concerning regulatory measures that would strengthen the BSE feed rule.*

2005 ..... *Second BSE-infected cow is discovered in the United States.*

2005 ..... *FDA issued proposed amendment to BSE feed regulation to prohibit use of certain high-risk cattle materials in food or feed of all animals.*

THE CHALLENGE

The discovery of a second BSE-infected cow in the United States, during FY 2005, added to CVM's challenge to strengthen controls that will prevent the spread of BSE through feed. (The first infected cow was discovered in December 2003.) BSE is a chronic, degenerative, always fatal neurological disease affecting the central nervous system of cattle.

FY 2005 Performance Goals

- ✓ Collect and analyze samples of domestic and imported feeds and feed ingredients to monitor for the presence of prohibited animal proteins (in conjunction with the Office of Regulatory Affairs [ORA]).
- ✓ Enforce the feed rule by conducting annual, targeted BSE inspections of all known renderers and feed mills processing products containing prohibited material (in conjunction with ORA).
- ✓ Allocate resources to extend BSE inspections into targeted segments of industries (e.g., animal feed salvaging, distributors, retailers, transporters, on-farm mixers, and ruminant feeds) subject to the BSE feed regulation but previously minimally inspected (in conjunction with ORA).
- ✓ Allocate resources to accomplish up to 8,760 BSE inspections; 3,760 inspections will be conducted by FDA investigators, and up to 5,000 inspections (4,100 planned State contract inspections and 900 partnership inspections) will be conducted by the States (in conjunction with ORA).
- ✗ Develop and initiate validation of an improved method for detecting prohibited animal proteins in feed using Real-Time PCR (Polymerase Chain Reaction) that will allow for the identification of up to four different prohibited species in a single reaction. Adapt the Real-Time PCR methodology to identify prohibited animal proteins in rendered materials from the European Union as well as materials rendered in the United States.

The PCR method has not been completed. We were unable to satisfactorily work out problems with the four species in one tube with a contracting firm in a timely fashion. Therefore, we are moving toward development of a real-time method with single species in a tube. Currently, we are conducting an exhaustive in-house testing of this method prior to beginning a validation study.

BSE belongs to a family of diseases known as transmissible spongiform encephalopathies (TSEs) that include several ruminant and non-ruminant animal diseases. Laboratory and epidemiological evidence strongly suggests that people can contract a human TSE, variant Cruetzfeldt-Jakob Disease (vCJD), by consuming food from BSE-infected cattle. In the absence of adequate controls, BSE could spread among the cattle population through feed ingredients derived from infected cattle.

FY 2005 Accomplishments

We continued to provide the expert scientific knowledge and review on BSE for the Agency. Much of our effort during the year focused on follow-up action related to the second BSE case, assistance to the Federal government in efforts related to the international marketing of U.S. beef, and steps toward strengthening our BSE feed regulation. We made significant progress in developing analytical methods that will enhance efficient, effective compliance with the regulation. Following are highlights of some of our achievements during the year just ended, as we focus on the FDA strategic priorities of protecting consumer and animal health, and efficient risk management.

RESPONDING TO THE SECOND BSE CASE IN THE UNITED STATES

In June 2005, the U.S. Department of Agriculture informed FDA that a cow in Texas tested positive for BSE. The animal's carcass was disposed of by incineration, and did not enter the human food or animal feed chains. Although the animal posed no risk to the animal feed supply, FDA, along with USDA's Animal and Plant Health Inspection Service, the Texas Animal Health Commission, and the Texas Feed and Fertilizer Control Service, conducted a feed investigation with two main objectives.

The first objective was to identify all protein sources in the animal's feed history that could potentially have been the source of the BSE agent. The investigation found that no feed products used on the farm since 1997 had been formulated to contain prohibited mammalian protein. The second objective was to verify that cattle of interest leaving the herd after 1997 were rendered at facilities that were in compliance with FDA's 1997 regulation that prohibits most mammalian protein in the feed for ruminants (the BSE feed rule). This part of the investigation involved visits to nine slaughter plants and eight rendering plants. The investigation found that all rendering plants were operating in compliance with the BSE feed rule. A review of the inspection history of each of these rendering firms found no previous violations.

STRENGTHENING THE BSE FEED REGULATION

As the fiscal year came to a close, FDA proposed new measures to help further protect consumers against the agent thought to cause BSE. The Agency proposed to amend the BSE feed regulation to prohibit from use in the food or feed of all animals certain cattle materials that have the highest risk of carrying the BSE-infectious agent. The materials include:

- the brains and spinal cords from cattle 30 months of age and older;
- the brains and spinal cords from cattle of any age not inspected and passed for human consumption;
- the entire carcass of cattle not inspected and passed for human consumption if the brains and spinal cords have not been removed;
- tallow that is derived from the materials prohibited by this proposed rule if the tallow contains more than 0.15 percent insoluble impurities; and
- mechanically separated beef that is derived from the materials prohibited by the proposed rule.

All of the proposed prohibitions, except for those related to tallow, have applied to ruminant feed since the regulation's adoption in 1997.

The removal of high-risk materials from all animal feed – including pet food – will protect against the transmission of the agent of BSE that could occur either through cross-contamination of ruminant feed with non-ruminant feed or feed ingredients during feed manufacture and transport, or through intentional or unintentional misfeeding of non-ruminant feed to ruminants on the farm. Although overall compliance with the BSE feed rule has been high, inspections have revealed some instances of cross-contamination and failure to label prohibited materials properly. Financial incentives for misfeeding exist in some circumstances. Regulatory action has been taken where problems were found, but preemptive action to avoid violations seems prudent.

We believe that the additional measures will make an already small risk even smaller. The proposed changes to the regulation build on a series of firewalls that include the BSE feed regulation, which prohibits the use of certain mammalian-origin proteins in ruminant feed (e.g., for cattle and sheep), but allows these materials to be used in feed for non-ruminant species.

STRENGTHENING THE BSE FEED REGULATION INSPECTIONAL EFFORTS

Inspections

Utilizing resources allocated by CVM in FY 2005 to the Office of Regulatory Affairs, FDA exceeded its goal and conducted 4,001 inspections. The States, based on available inventory of firms conducted an additional 3,309 inspections for a total of 7,310. The inspections conducted by FDA and the States included the inspection, analysis, and follow-up of all 580 firms known to process products containing prohibited material. That total also included as many inspections of related industry firms (e.g., animal feed salvagers, distributors, and retailers) as could feasibly be accomplished. We also worked with ORA in the collection, analysis and follow-up of 838 domestic and 458 imported product samples. In summary, we believe that the FY 2005 performance goals related to BSE inspections were accomplished.

Training

CVM continued to provide BSE inspection training to FDA investigators as well as State inspectors during the fiscal year. We conducted several one-day training courses across the country, including courses in Florida, North Carolina, Idaho, and Oklahoma. CVM also had opportunities in other settings, including meetings of State feed control officials, to assist in training or to provide an update on BSE activities.

INTERNATIONAL BSE ACTIVITIES

We have provided personnel and expertise on BSE and animal feed issues to the U.S. Department of Agriculture in support of its efforts to reopen foreign markets for U.S. beef. Center representatives met during FY 2005 with numerous groups from foreign governments to discuss the BSE inspection program and our feed regulations. Most of these meetings were stimulated by the decisions of a number of nations, following the discovery of the first BSE-infected cow in the U.S., to stop purchasing beef originating from the United States. These countries have been evaluating the regulation of beef and animal feed in the United States, to guide their decisions on reopening their markets to U. S. beef. During FY 2005, we met in the United States with delegations from Korea, Taiwan, Ireland, and a number of Eastern European countries, and we accompanied U. S. delegations on trips to Canada, Japan, Korea, and China.

DEVELOPING ANALYTICAL METHODS FOR DETECTING PROHIBITED MATERIALS

The availability of practical, validated methods to detect protein from different animal species could improve effectiveness and efficiency in the enforcement of the BSE feed regulation. Methods to detect mammalian protein have been available for some time, but because not all mammalian proteins are prohibited from ruminant feed, methods are needed to identify protein from prohibited species such as cattle. The development and use of such methods would be consistent with the FDA strategic plan priority of targeting limited resources for maximum protection.

Real-Time PCR Methods

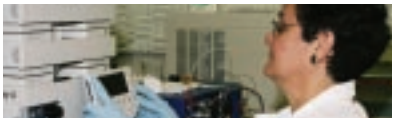
During FY 2005, we continued the development of real-time polymerase chain reaction (PCR) methods for identification of appropriate species – bovine, sheep/goat, and deer/elk. ("Real-time" means that we can detect the presence of prohibited material as the reaction is taking place, so we do not have to further process the sample.) The method will detect prohibited materials prepared by either U.S. or European Union rendering processes. After discussions with analysts in FDA's Office of Regulatory Affairs who conduct PCR analyses of animal feed, we modified our research on the real-time PCR method. We are working now to simplify the entire procedure from start to finish, thus making it very user friendly. We have identified primers[4] for the appropriate species and are working on combining all components of the procedure, excluding the actual instrumentation part, into a single package. Once we have completed the in-house evaluation of this revised PCR method, we will conduct a validation study in preparation for use in the field. The Agency is currently using a traditional PCR method (not a real-time PCR) to support positive findings of animal protein by the microscopy method.

BSE research: Developing methods to detect prohibited material

Commercial Diagnostic Kits

Commercially available diagnostic test kits marketed for the detection of ruminant proteins in animal feed can be important tools for surveillance and quality assurance. FDA does not have preclearance authority over such kits, but undertook evaluation of two of the kits in FY 2004, to assess the accuracy of claims made. We completed the evaluation of a third such kit in FY 2005. Like the two diagnostic tests previously evaluated, this test was much less sensitive than the methods the Agency uses (microscopy and PCR) for analysis of animal feed. We also identified labeling issues that need to be addressed. An evaluation of a fourth commercially available diagnostic test will be initiated in FY 2006.

[4] PCR primers are short sections of DNA that mark the beginning and end of the section of the DNA template that is being copied by the PCR process. If they are specific to a known sequence of DNA nucleotides, PCR primers can identify the species from which the tested material is derived.



Avoiding Unsafe Drug Residues in Human Food

Animal Drug Residue Milestones

1958 ..... *Food Additives Amendment passed; applied to animal drugs that cause residues in edible products, and included the Delaney anti-cancer clause.*

1962 ..... *Congress amended Delaney Clause to allow approval of carcinogenic animal drug that causes "no residue" in edible products.*

1968 ..... *Animal Drug Amendments eliminated the need for separate drug and food additive approvals for drugs used in food-producing animals. New section 512 included requirements for development of regulatory methods and establishment of tolerances and withdrawal times.*

THE CHALLENGE

Improper use of approved drugs or use of unapproved drugs in domestic animals can result in unsafe residues in meat, poultry, seafood, milk, and honey. Firms or individuals who repeatedly present animals for slaughter that are adulterated with illegal drug residues may represent a significant public health risk. In fact, investigation of repeat violators is a top priority. In addition, investigating first-time violations of residues from drugs prohibited from extra-label use in food animals, residues of drugs not approved for food animal use, and very high-level drug residues are high priorities for investigation. Also, we are challenged by the FDA Strategic Plan's emphasis on the need for safety oversight to catch up with the rapid growth in the volume of imported products, especially seafood, that are under FDA's jurisdiction.

FY 2005 ACCOMPLISHMENTS

The following summarizes our FY 2005 efforts to avoid unsafe residues in meat, milk, seafood, and honey.

FY 2005 Performance Goal

Continue to develop and validate multi-residue drug screening methods (for chemical and microbiological hazards), and continue to conduct method validation studies for the approval of applications for new drugs for food-producing animals.

ENFORCEMENT TO CONTROL DRUG RESIDUES IN MEAT

Actions Against Tissue Residue Violators

Under CVM's direction, FDA's Office of Regulatory Affairs, and State agencies working on the Agency's behalf under contracts or cooperative agreements, investigated tissue residue violations during the year. FDA issued tissue residue-related Warning Letters. Enforcement actions resulted in consent decrees of injunction against several dairy farms that had marketed cows and calves whose edible tissues contained illegal drug residues.

We provide an example of the enforcement actions in this case history. The U.S. Department of Agriculture's Food Safety and Inspection Service (FSIS) found 13 illegal tissue residues in edible tissues of seven animals from a California dairy sampled between December 1997 and January 2004. The drug residues included antibiotics such as penicillin, gentamicin, neomycin, and sulfadimethoxine that were either above the permitted tolerance levels or had no established tolerance. These drug residues have a potential for adverse effects on human health. We approve new animal drugs only after establishing a specified time period to withdraw an animal from treatment prior to marketing. This ensures that the drug has depleted from edible tissue to a level that will not present harm to the consuming public. Investigation by FDA's San Francisco District Office documented the dairy's failure to maintain controls to prevent illegal residues in animals delivered for slaughter.

In April 2005, the dairy's owner consented to a permanent injunction. Under the terms of the consent decree, which was filed in the U.S. District Court for the Eastern District of California, the dairy must implement residue avoidance systems including segregation/quarantine and identification of treated animals, maintenance of medication/treatment records, and accountability for drug inventory. The firm is also required to follow label directions for drug use including labeled time periods for withdrawal prior to slaughter.

Expansion of Tissue Residue Compliance Program

We implemented a major revision of the Tissue Residue Compliance Program[5] in August 2005. Because firms or individuals that repeatedly present adulterated animals for slaughter may represent a significant public health risk, CVM will now issue assignments to the FDA District Offices requesting an FDA on-site investigation for each repeat violator. In addition to directions for investigating residues in meat and poultry, the Compliance Program now includes instructions for investigating residues in seafood and other animal-derived foods such as honey.

Residue Violation Information System (RVIS) Update

An interagency database shared with FSIS, the Residue Violation Information System (RVIS) was successfully converted during FY 2005 to a web based application that uses an Oracle Relational Database. The database contains information on all tissue residue violations/violators identified since 1988. This modernization effort was completed to make RVIS easier to understand and operate, to eliminate the need to install customized software on user computers, and to make it location independent. We provided three days of training on the use of the updated system to FDA's Tissue Residue Monitors in May 2005.

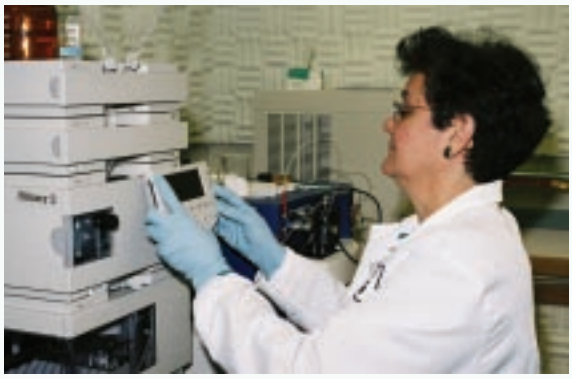
[5] Illegal Residues in Meat, Poultry, Seafood and Other Animal Derived Foods, Compliance Program 7371.006

CONTROLLING DRUG RESIDUES IN AQUACULTURED PRODUCTS

The United States is a major market for food products from foreign aquaculture facilities. Discussions with foreign governments and other intelligence have revealed that many drugs used in the production of these products are not approved in the United States, and some, e.g., chloramphenicol and nitrofurans, are specifically prohibited for use in food animals in the United States. Thus, potentially unsafe animal drug residues may be contained in imported aquaculture food products. FDA has not adopted tolerances or testing methods for many of these drugs to determine if there are any residues of such drugs in seafood.

In FY 2001, CVM awarded a five-year contract for data collection on aquaculture drug use in countries that exported seafood to the United States, the development of a database for this information, and a risk assessment on the information collected. This information would be used to assist in prioritization of residue detection method development, and to enhance the drug residue seafood sampling program administered by FDA's Center for Food Safety and Nutrition (CFSAN). The performance period for the contract is nearing completion. We expect the final report on the risk assessment to be completed by the end of calendar year 2005.

CVM continues to give CFSAN technical support on drug use in aquaculture by providing guidance on program sampling priorities and methods development.



Conducting a nitrofuran detection test

TRAINING FOR MILK SAFETY

CVM provided an instructor for three week-long training courses in FY 2005. The training courses were part of the milk safety cooperative program agreements between the FDA, State agencies, and National Conference of Interstate Milk Shipments (NCIMS). The courses, which provided continuing education credits, were attended by public health officials and registered sanitarians from State milk regulatory departments (agriculture and/or health departments), FDA milk specialists and district investigators, university faculty, members of State veterinary licensing regulatory boards, and members of the dairy industry. The courses included training on dairy farm sanitation and inspection, proper animal drug use, residue avoidance, labeling, storage, and updates on important public health issues such as BSE, tissue residues, drug approvals, and residue testing.

FOOD SAFETY MEETING

We hosted the third National Food Safety Meeting in St. Louis, MO, in May 2005. The meeting included representatives from FDA's District Offices, FSIS, USDA's Animal and Plant Health Inspection Service, and cooperating State agency officials. Topics included zoonotic diseases, animal identification, the Animal Feed Safety System, import tolerances, antibiotic resistance, USDA's residue testing plan and policies, and other tissue residue-related topics.

RESEARCH TO SUPPORT SAFETY OF DRUG RESIDUES IN MEAT

During FY 2005, CVM scientists continued to study the correlation of drug residue levels in tissues and fluids of beef steers, for use in the development of rapid screening test kits. Pioneering work by CVM scientists in using laparoscopic surgical techniques to obtain kidney samples in standing animals made much of this work possible. Using highly sensitive laboratory analysis techniques such as tandem mass spectrometry, also developed by CVM scientists, we were able to identify the mathematical relationship between penicillin levels in the animals' kidney tissue and in the much more readily obtained blood and urine. Use of rapid screening tests by producers and feedlot operators can indicate if the penicillin has been depleted to a sufficient extent to allow slaughter of the beef steer without the meat having unsafe drug residues.

CVM scientists also completed their study of the long-term kidney depletion of gentamicin in beef steers. Quantifiable levels of gentamicin were present in the kidney cortex tissue for at least 10 months following the last systemic dose of this antibiotic. The concentration of gentamicin in kidney tissue biopsy samples demonstrated a uniquely shaped depletion curve, which was partially correlated with the concentration of gentamicin in urine. Gentamicin was detectable in the animals' urine for at least four months. This research provides the basis for a practical preslaughter method to determine misuse of this antibiotic.

CVM provided FSIS with the final reports of these studies. The research was partially funded by FSIS to support its Hazard Analysis and Critical Control Points (HACCP) quality programs.

Ensuring Feed Safety

Milestones in Feed Regulation

1906-1938 ..... *The earliest veterinary-related regulatory actions under the 1906 Act were primarily directed at misbranded animal feeds.*

1968 ..... *Animal Drug Amendments authorized approval of medicated feeds, eliminating the need for separate approval of medicated feeds as drugs.*

1996 ..... *Congress authorized feed mill licensing, eliminating the need for medicated feed applications, as part of the Animal Drug Availability Act.*

1996 ..... *The Animal Drug Availability Act also authorized approval of feed-use drugs as Veterinary Feed Directive drugs, i.e., limited to use under a veterinarian's supervision.*

THE CHALLENGE

Threats to the safety of the nation's animal feed supply could come from several sources, including bioterrorism. Contaminants and unsafe additives in animal feed can harm the animals, as well as humans who consume animal products, and can adversely affect the nation's food and feed supplies. Improper manufacture of animal feeds can also result in health problems for animals and humans.

FY 2005 ACCOMPLISHMENTS

Following are highlights of our FY 2005 accomplishments with regard to feed safety. In addition to the actions described below, we completed a variety of ongoing assignments, including processing 144 medicated feed mill licensing applications (firms that manufacture certain medicated feeds are required to be licensed).

FY 2005 Performance Goals

- ✓ Maintain biennial coverage by inspecting 50% of the registered animal drug and feed establishments (in conjunction with ORA).
- ✓ Develop and publish draft AFSS framework document for public comment.
- ✗ Develop work products that address identified and agreed upon gaps in the Agency's animal feed regulatory program for public comment.

A revised framework document is being prepared. The revised document will more clearly identify the gaps that need to be addressed and the work product for each gap. The revised document should be available for additional public review next fiscal year.

- ✓ Complete at least 80% of FY 2005 Food Additive Petitions, Adverse Event Report evaluations, GRAS/GRAE Petitions, Warning Letters, Untitled Letters, responses to Field inquiries and recommendations, general correspondence, and Congressional correspondence input to the Office of Executive Programs.
- ✓ Continue to develop analytical methods to detect the presence of prohibited animal substances that could be introduced into U.S. animal feed supplies by bioterrorists. (This goal applies both to animal feed safety and bioterrorism, and therefore is listed in both sections.)

RISK-BASED SYSTEM – ANIMAL FEED SAFETY SYSTEM (AFSS)

CVM is developing a nationwide, comprehensive risk-based system that would be preventive. We are designing the Animal Feed Safety System to detect hazards before feed products are distributed, and thus minimize detrimental animal and human health effects. FY 2005 accomplishments were as follows.

AFSS Framework Document

A team consisting of officials from CVM, FDA's Office of Regulatory Affairs and Office of the Commissioner, as well as State officials, drafted this document after considering comments received from a public meeting held in September 2003. FDA published a notice of availability of the framework document in February 2005. The document covers regulation of the labeling, production, and distribution of all feed ingredients and mixed feeds at all stages of manufacture, distribution, and use. It sets out seven operating principles and four major components for the AFSS. The document explains the purpose and goals for each component, identifies gaps within each component, and specifies the enhancements necessary to make the AFSS comprehensive and risk-based. It also includes a general description of the work products necessary to address each gap. Because AFSS will be a risk-based system, CVM is developing a risk-ranking method that can be used to identify and determine the relative levels of risk from feed contaminants.

A meeting of CVM's Animal Feed Safety System project team

Closing the Gaps

We presented the AFSS draft for discussion at a public meeting in Omaha, NE, in April 2005. As a follow-up to the public meeting, we are developing work products to address the identified gaps in the Agency's animal feed regulatory program. Eight gaps have been preliminarily identified, with one work product completed. The remaining work products should be finished during calendar year 2006. We will make these work products available for public comment.

SAFETY REVIEW OF FEED INGREDIENTS

Food Additives

CVM is responsible for the review and approval of new substances intentionally added to animal feed that are not generally recognized as safe (GRAS). We had several food additive petitions under review during the year, including petitions for coated urea and conjugated linoleic acid (CLA). CLA is a proposed new fatty acid source for swine. CLA has been associated with health benefits when consumed by humans, and researchers have been trying to increase the CLA content in animal products as a way of increasing human CLA intake.

Feed Ingredients

The *Official Publication* of the Association of American Feed Control Officials (AAFCO) contains a list of feed ingredients with their definitions. Many of these ingredients are not approved additives or GRAS; however, we do not object to the listing of certain ingredients provided there are no apparent safety concerns. During FY 2005, we reviewed and accepted several ingredient definitions, including definitions for two direct-fed microbial species, a novel sweetener (neohesperidin dihydrochalcone) in piglet diets, taurine in dog diets, selenium yeast for use in four new species (goats, sheep, horses, and dogs), and two enzymes. Interest in the feed use of enzymes continues to increase. We reviewed and accepted the safety of protease, and a phytase that may have positive environmental effects.

TRAINING AND OUTREACH

Medicated Feed GMP Training

We conducted a medicated feed Good Manufacturing Practice (GMP) training program for the North Carolina Department of Agriculture and FDA Atlanta District investigators in January 2005. Because we had a small group of experienced investigators, we were able to take a novel approach, customizing the material to meet their needs and compressing the course into one day.

Outreach to Stakeholders

Our education and outreach efforts during the year were diverse. For example, we posted information on the CVM website to answer frequently posed questions concerning the use of monensin in the feed of dairy cows. The FY 2005 approval of the drug for a new indication, increased milk production efficiency in dairy cows, generated the questions. We also published an article titled "What are the Rules Concerning the Use of Color Additives in Animal Feeds and Pet Foods?" in the January/February 2005 *FDA Veterinarian*, to help consumers better understand FDA's regulation of feed ingredients. We also reviewed and commented on or otherwise processed 83 documents pertaining to animal feed (including medicated feed), feed safety, and labeling. Our document review work included requests for regulatory opinions, consumer inquiries, and Freedom of Information Act requests.

COMPLIANCE CHALLENGES IN ANIMAL FEED SAFETY

Feed Contaminant Incidents

We were involved in investigation of a number of feed contaminant episodes including:

- An incident in Maryland in which six dairy cattle were clinically diagnosed with lead poisoning suspected to have resulted from lead shot from an adjacent hunt club firing range. Action was taken to withhold milk, found to contain over 100 parts per billion of lead, from the market.
- Deaths of California dairy cows, determined to be from *Clostridium botulinum* toxin type C, most likely from silage.

- Elevated levels of heptachlor expoxide in 40 head of Missouri beef cattle, determined to be the result of past usage of heptachlor that was leaching from the soil.

Field Assignments Related to Microbiological and Chemical Contaminants

On the basis of continuing reports of contamination of pet food and animal feed with *Salmonella*, the Center conducts surveys every year to determine the prevalence of contamination with *Salmonella* as well as other organisms. During FY 2005, we issued a field assignment for a Survey to Determine the Prevalence of Foodborne Pathogens (*Salmonella*, *E. coli*, and *Enterococcus*) in Complete Mixed Feeds for Market Swine. Information from the surveys helps the Center target educational plans and enforcement actions to protect animal and human health.

The Center has also issued assignments to collect data on contamination of feed and feed ingredients with dioxins, which can cause a broad range of adverse effects such as enhanced tumorigenicity and immune suppression. During FY 2005, we issued an assignment for a nationwide survey to assess dioxin levels in rendered fat from swine, cattle, poultry, and mixed animal species; in yellow grease; and in agents (such as clay and diatomaceous earth) used to filter and/or bleach mammalian and poultry fats. We presented data – from samples collected in FY 2001-2004 – on dioxin levels in grains, grain byproducts, fishmeal, fish oil, and forages at an October 2004 scientific meeting in Greensboro, NC.

Revision of the Feed Contaminants Compliance Program

We initiated revision of the program, to clarify testing priorities for mycotoxins in feed ingredients and feeds, and sample collection and analysis procedures for microbiological samples (*Salmonella* and *E. coli 0157:H7*).

Feed Recalls

The Center handled 83 feed recall events during FY 2005. Twenty of these recalls related to drugs used in feeds. Six feed recalls were due to BSE feed regulation issues – the feed contained or could have contained prohibited material and did not have the required caution statement.

Medicated Feed Mill Inspections

During FY 2005, FDA and State inspectors completed inspections of more than half of the approximately 1,100 FDA-licensed medicated feed mills in the United States.

RESEARCH RELATED TO CHEMICAL CONTAMINANTS IN ANIMAL FEEDS

Methods Development for Feed Contaminants

Contamination of animal feeds by inappropriate drug levels, insecticides, fungal mycotoxins, or other harmful chemicals causes potential health risks. Many compounds of concern are amenable to analysis by liquid chromatography-tandem mass spectrometry (LC-MS/MS). Methods are being developed that will combine simple liquid extractions of animal feed with powerful LC-MS/MS surveillance for a wide range of the compounds of concern:

- In the first phase of method development (during FY 2005), we validated a procedure for surveillance of 27 animal drug compounds from nine chemical classes.
- Work is underway to increase the number and range of target compounds; the final methods may include over 100 potential chemical contaminants. Chemists from our Office of Research are now partnering with analysts from FDA's Office of Regulatory Affairs and the Environmental Protection Agency to expand this approach to include pesticides that are used for pest control in feed mills and that have potential for deliberate contamination (during FY 2005) and fungal and other toxins (during FY 2006).

The LC-MS/MS approach should enable efficient surveillance for many suspect compounds. We are using a standardized set of model feeds to evaluate the new methods, based on the wide range of protein, carbohydrate, fiber, oil, and moisture content that might be present.

Screening Tests for Aflatoxin

Aflatoxins are naturally occurring mycotoxins that can contaminate corn and other grains, often leading to a significant loss of feed and the potential for harm to animals consuming the feed. In addition, intentional contamination of feed with aflatoxins may serve as a potential route for bioterrorism. Existing aflatoxin screening tests have been validated for use in corn. In FY 2005, we evaluated two commercially available rapid screening test kits, to determine whether the tests could detect the presence of aflatoxins in finished feeds. This would allow the detection of aflatoxin added after the raw commodity (corn) is tested. We evaluated a color change test used to detect aflatoxin above the tolerance level. The second rapid test we evaluated is used in conjunction with an aflatoxin-specific liquid chromatography test, which measures the quantity and identifies the type of aflatoxin. We expect to complete the analysis, to determine whether the tests can be used in finished feed, during FY 2006.

Protecting Against Bioterrorism

Milestones in Bioterrorism Regulation

2002 ..... *Congress passed the Public Health Security and Bioterrorism Preparedness and Response Act (the Bioterrorism Act) following the events of September 11, 2001.*

2003 ..... *FDA adopted interim final regulations requiring prior notice of imported human and animal food shipments, and registration of human and animal food facilities.*

2004 ..... *FDA adopted regulations concerning administrative detention of human and animal food, and records relating to human and animal food.*

2005 ..... *FDA adopted final regulation requiring registration of human and animal food facilities.*

THE CHALLENGE

There is widespread concern that microbial and/or other toxic agents could be used in the food chain as weapons to harm human and animal health. Bioterrorism against the human food and animal feed supplies would also harm the U.S. economy. FDA-regulated products such as animal drugs would play a central role in countering the effects of such terrorism. FDA is responsible for implementing provisions of the Bioterrorist Act relating to protection of the nation's food and drug supplies. CVM is working with other Federal agencies to help the country prepare for a biological emergency, natural disaster, or terrorist attack by making sure there is a safe and adequate supply of animal drug products and a safe animal feed supply system.

FY 2005 ACCOMPLISHMENTS

As we continue to define our role and goals with respect to bioterrorism, we have been active during the past year with respect to several initiatives that are in line with the FDA's Strategic Action Plan priorities of preparing for and effectively responding to bioterrorism and other public health emergencies.

FY 2005 Performance Goals

- Perform prior-notice import security reviews on 38,000 food and animal feed line entries considered to be at high risk for bioterrorism and/or present the potential of a significant health risk (in conjunction with ORA).

Meeting this goal accomplishes the FDA strategic goal of ***preparing for and effectively responding to bioterrorism and other public health emergencies by increasing capacity to respond to attacks and improving the safety of food, drugs, biological products, and medical devices****.*

- Continue to develop analytical methods to detect the presence of prohibited animal substances that could be introduced into U.S. animal feed supplies by bioterrorists. (This goal applies both to animal feed safety and bioterrorism, and therefore is listed in both sections.)

ENFORCING THE BIOTERRORISM REGULATION REQUIREMENTS

Regulatory Overview

FDA has issued several implementing regulations relating to food security as required by the Bioterrorism Act of 2002. Two of these regulations were adopted during FY 2005: a recordkeeping regulation, issued in December 2004; and a final rule concerning registration requirements for food facilities, published in September 2005 (the Agency had adopted an interim final registration rule in October 2003). A brief summary of the bioterrorism rules, their implication for animal food, and CVM's FY 2005 accomplishments follows.

Recordkeeping Requirements

The recordkeeping rule requires persons who handle food, including feed and pet food, to maintain records that document the source of the food or ingredients and the destination for the products. FDA inspectors will need access to these records to investigate credible threats of serious adverse health consequences or death to humans or animals.

Prior Notice Requirements

The prior notice interim final rule specifies that those who import food (including animal feed and pet food) are to provide detailed information about the products before they are brought into the United States. Having prior notice allows inspection of high-risk products before entry. Only a small percentage of the nation's animal feed and feed ingredients are imported, and only a small percentage of the imported foods considered to be high risk are intended for animals. Nevertheless, the Agency monitors carefully to identify shipments that may ultimately threaten the nation's food chain via livestock and poultry, or our pet population.

CVM representatives participated during FY 2005 in weekly Prior Notice Working Group conference calls, providing advice and security reviews on animal feed and pet food entries considered to be high risk. The group shares information on imported food products.

Registration Requirements

FDA's registration regulation requires firms that manufacture, process, pack, or hold food for human or animal consumption to register with the Agency. This information will assist with prompt identification of food processors and other establishments, in the event of deliberate or accidental contamination of the food supply. FDA and State investigators are checking with feed manufacturers during inspections (such as medicated feed GMP inspections) to determine whether the firms are aware of that requirement and have complied. CVM has developed a brief presentation, to be used during training sessions, that explains what the investigators should look for when doing an inspection, and provides information on how to advise the firm if it is not yet registered.

Administrative Detention Procedures

The Bioterrorism Act authorizes FDA to administratively detain suspect food, and the regulation sets forth detention procedures. The authority applies to food for which the Agency has credible evidence or information that it presents a threat of serious health consequences or death to humans or animals. This new authority likely will be applied mainly to food that is in domestic commerce, because the Agency has previously existing detention authority that also applies to imported food products.

DEVELOPING AND TESTING EMERGENCY RESPONSE PLANS

TOPOFF 3 Exercise

The U.S. Department of Homeland Security's Top Officials Three Exercise (TOPOFF 3) was a congressionally mandated exercise designed to strengthen the nation's capacity to prevent, prepare for, respond to, and recover from large-scale terrorist attacks involving weapons of mass destruction. The most comprehensive terrorism response exercise ever conducted in the United States, TOPOFF 3 consisted of a two-year cycle of seminars, planning events, and exercises culminating in a full-scale exercise in April 2005 that simulated a coordinated terrorist attack involving biological and chemical weapons. The exercise involved numerous Federal departments and agencies, the States of Connecticut and New Jersey (States request to participate in TOPOFF and two are selected for each exercise cycle), the United Kingdom, Canada, and representatives from the private sector.

CVM representatives participated in TOPOFF 3. One of the challenging agents was plague, which may be transmitted and perpetuated by the companion animal population, with fleas as a vector. CVM worked closely with CDC and other veterinary-allied groups in developing a public guide entitled "Controlling Fleas on Your Pet: Recommendations for Pet Owners." This useful guide is now available for possible future use by public health authorities.

National Preparedness Goal

CVM assisted the Department of Homeland Security and other agencies with the completion of a draft National Preparedness Goal and the Target Capabilities list that will help States prepare for a wide range of emergencies. The emergencies include accidental or deliberate disease outbreaks, natural disasters, and nuclear and contamination events involving food and livestock. This is a major ongoing effort with the States and other impacted groups.

Coordinating Response to Agroterrorism Threats

CVM participated during the year in the Agricultural Intelligence Group. The group meets regularly to exchange information and ideas about food security, and to discuss ways in which the participating agencies can best utilize their combined skills, technology, and resources to prevent and respond to agroterrorism threats. Participants include representatives of the FBI, CIA, USDA, Department of Homeland Security, and Department of Defense, in addition to FDA.

EDUCATING STAKEHOLDERS

During the year, we educated constituent organizations as to the need for, and how to perform, vulnerability assessments of animal feed and feed ingredient production facilities. These organizations included the Quality Council of the American Feed Industry Association, the National Renderers and Protein Blenders Association, and the U.S. Animal Health Association.

CVM played an integral role in helping representatives of the swine industry present a series of workshops and meetings called "A Strategic Conversation: Swine Business Sustainability Following An Animal Agriculture Emergency."

RESEARCH RELATED TO BIOTERRORISM

As discussed in the Animal Feed Safety section, we made considerable progress during the year in developing analytical methods to detect the presence of toxins, drugs, pesticides, and other substances that could be introduced into U.S. animal feed supplies by bioterrorists. In addition, intentional contamination of feed with animal pathogens is a significant concern with regard to agri-terrorism.

Some pathogens are present in the environment as part of the normal ecosystem but not at population densities that would allow infection. To make decisions about potential cases of intentional contamination with naturally occurring pathogens, we need to know the background levels of these organisms one would expect to recover during typical random sampling. Office of Research scientists are initiating survey programs to assess background levels of the animal pathogen *Bacillus anthracis* that can routinely be recovered from animal feeds. These data will provide a baseline for comparison against levels in feeds where intentional contamination has occurred.

A second phase of this work will test the performance of rapid methods for detecting anthrax in feed samples identified as positive by standard cultural methodologies. Animal feed commodities are often retained for a very short period of time at feed manufacturing facilities, and thus rapid detection methods are essential for timely decision-making with regard to the ultimate disposition of these materials.

Assuring the Safety of Biotechnology Products

Biotechnology Milestones

1990s ..... *CVM began to investigate biotechnology products produced by animals for food production and for medical applications under investigational new animal drug files.*

1992 ..... *FDA issued a statement of policy on new (genetically modified) plant varieties, which applied to plant materials intended for animal feed as well as human food.*

1993 ..... *CVM approved a recombinant bovine somatotropin (rBST) product, the first approval of an animal drug produced by biotechnology, for increased milk production in dairy cattle.*

2001 ..... *CVM asked animal producers to withhold from the market food and feed products derived from clones and their progeny pending completion of a safety assessment. CVM initiated a contract with the National Academy of Sciences/National Research Council (NAS/NRC) to conduct risk characterization for animal biotechnology and cloning, and began preparation of its own animal clone risk assessment.*

2002 ..... *CVM co-sponsored a public meeting on animal cloning with Pew Initiative on Food and Biotechnology. NAS/NRC reported on its contract with CVM with the publication,* Animal Biotechnology – Science Based Concerns.

2003 ..... *CVM met publicly with the Veterinary Medicine Advisory Committee to preview its animal clone risk assessment.*

THE CHALLENGE

The application of biotechnology to the production of animals and products derived from animals continues to grow in diverse directions. Animal biotechnology includes both genetic engineering and cloning. Animal cloning is seen as a means of expanding populations of cattle, swine, and goats with desired phenotypes. Genetic engineers are investigating broader ranges of applications in animals, from BSE-resistant cattle, to production of biomedical products secreted into transgenic chicken eggs and transgenic goats, to pigs as sources of organ transplants. Producing animals through biotechnology raises potential food and animal safety issues, and CVM needs to have a thorough understanding of the scientific and risk issues that the two kinds of animal biotechnology present.

FY 2005 ACCOMPLISHMENTS

In addition to working on continuing activities, such as reviewing products of plant biotechnology, our biotechnology-related activities during FY 2005 involved participation in international efforts to develop innovative resource documents.

RISK ASSESSMENT FOR GENETICALLY ENGINEERED ATLANTIC SALMON

FY 2005 saw the development, with significant U.S. government leadership that included CVM representatives, of an international project to assist individual countries in making environmental risk assessments of genetically engineered Atlantic salmon. CVM members of the U.S. delegation are providing expertise and leadership for this project. We helped organize and provide speakers for a December 2004 Moscow workshop to study the feasibility of the project. The project sponsor, the Organization for Economic Community Development (OECD), found that it was feasible to undertake the project. As a result, CVM provided a co-chair and an additional delegate for the Steering Committee effort to prepare an operational plan. A second workshop, held in Trondheim, Norway, provided a forum for outlining in detail a consensus document on the biology of Atlantic salmon. The consensus document will provide factual information on the ecology of Atlantic salmon. It will serve as the comparator against which genetically engineered Atlantic salmon will be analyzed, taking into consideration the specific environmental conditions under which genetically engineered Atlantic salmon may be introduced either accidentally or intentionally.

The Atlantic salmon is the first animal to be considered by OECD for this treatment, because there is an expectation that genetically engineered Atlantic salmon may be the first genetically engineered animal to be approved for food use. If this risk assessment project is successful, consensus documents may be developed for other species, particularly fish grown by aquaculture, much like the series of consensus documents that have been developed for genetically engineered plant species.

INTERNATIONAL DEVELOPMENT OF FOOD SAFETY GUIDELINES FOR RECOMBINANT DNA ANIMALS

CVM participated during the year in the 5th Session of the Codex Alimentarius Ad Hoc Intergovernmental Task Force on Foods Derived from Biotechnology, sponsored by FAO-WHO. The Task Force agreed to develop a *Guideline on the Food Safety Assessment of Food Derived from Recombinant-DNA Animals*. The Task Force established a Working Group to develop a draft guideline, and asked Australia and Japan to lead the work. The United States is a member of the Working Group and will participate in drafting the guideline.

REVIEW OF BIOTECHNOLOGY-DERIVED PLANT VARIETIES

Utilizing a voluntary notification system, FDA reviews the safety of biotechnology-derived plant varieties that have been developed for traits such as herbicide resistance, insect pest resistance, enhanced nutrient availability or modification of nutrient composition (e.g., high laurate canola and high oleic acid soybeans). Although not all of the new varieties are used in animal feed, CVM partners with FDA's Center for Food Safety and Applied Nutrition in the review of all of the varieties as the notifications are for both animal feed and human food.

During the past year, we participated in the review of five of the new submissions received by the Agency. This review included completion of consultations with the sponsors of new varieties of alfalfa and cotton that express a protein that makes these plants herbicide tolerant, a cotton variety whose seed expresses a protein that imparts resistance to certain types of insect pests, and two corn varieties that are both herbicide and pesticide resistant. We also contributed to the draft guidance entitled *Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use* that the Agency published in November 2004.

On the international scene, we collaborated with Canada and the UK in completing a *Consensus Document on Compositional Considerations for New Varieties of Alfalfa and Other Temperate Forage Legumes: Key Feed Nutrients, Anti-nutrients and Secondary Plant Metabolites*. We also collaborated with Finland and Germany on completing a *Consensus Document on Compositional Considerations for New Varieties of Barley (Hordeum Vulgare l.): Key Food and Feed Nutrients and Anti-Nutrients*. These consensus documents serve as scientific references to the international community, regulators, and private industry in evaluating bioengineered varieties of these crops.

Additional Surveillance and Compliance Actions To Protect Public and Animal Health

Surveillance and Compliance Milestones

1951 ..... *Durham-Humphrey Amendments authorized limitation of human drugs to prescription use. FDA continued to restrict, by regulation, certain veterinary drugs to use under a veterinarian's supervision.*

1962 ..... *Drug Amendments provided authority to:*

- *inspect manufacturing establishments;*
- *require compliance with current good manufacturing practice in the manufacture of drugs;*
- *impose drug listing and drug manufacturer registration requirements; and*
- *regulate prescription drug advertising.*

1977 ..... *FDA introduced its Bioresearch Monitoring Program initiative.*

1980s ..... *Two Federal appellate courts held that drugs used for veterinary compounding are not exempt from the animal drug approval requirements.*

1994 ..... *The Animal Medicinal Drug Use Clarification Act authorized extralabel use of approved drugs in animals, under certain restrictions.*

THE CHALLENGE

Surveillance and compliance activities are key parts of our efforts with regard to antimicrobial resistance, BSE, drug residues, feed safety, and other crosscutting issues described above. We have had challenges in additional areas that are related to our core functions of compliance-related actions and post-approval monitoring. These challenges include monitoring to assess post-approval drug safety, taking steps to ensure proper manufacture of approved drugs, regulating animal drug compounding and the marketing of unapproved drugs, and acting against other threats to public and animal health.

FY 2005 ACCOMPLISHMENTS

Following are highlights of our accomplishments during the past fiscal year. We completed a number of undertakings during the year in addition to those described below. For example, we participated with others in FDA in producing the last phase of the Pharmaceutical Inspectorate Training Course in August 2005. This undertaking supports FDA's priority of modernizing the health care system through improved drug manufacturing practices.

ADVERSE DRUG EXPERIENCE

Heartworm Drug Review

CVM worked with the manufacturer of ProHeart® 6 (sustained release moxidectin) to voluntarily recall the drug from the market due to concerns about serious adverse reactions associated with the product that could not be mitigated. In January 2005, the Veterinary Medicine Advisory Committee (VMAC) reviewed the Center's risk management strategy and concluded that the drug should remain off the market until FDA's concern about adverse reactions associated with the product could be resolved. ProHeart® 6 is an approved injectable sustained-release heartworm prevention product for dogs. Heartworm disease is a serious and potentially fatal condition of dogs, cats, and other species of mammals.

Adverse Drug Experience (ADE) Review

One of FDA's Strategic Plan priorities is to increase attention on adverse events connected with drug use. During FY 2005, we received over 35,000 adverse experience reports, an increase of approximately 5,000 from FY 2004. Even though we had no increase in staff, we were able to review all of the approximately 17,000 ADEs related to tier 1 and 2 drugs (the highest priorities) in the required timeframe. We were also able to review approximately 1,000 tier 3 ADEs.

The Center began participation during the year in a pilot program that is intended to facilitate the electronic submission of adverse drug experience reports. When fully instituted, this program will enhance the Center's ability to process and evaluate adverse drug experience reports. We provide additional details on this initiative (PV-Works Pilot) in the section on achievement of management goals.

PUBLIC HEALTH ACTIONS

Salmonella in Turtles

During FY 2005, we experienced an increase in the number of complaints pertaining to the illegal sale of small turtles with a carapace (thick shell that covers the back of a turtle) of less than 4 inches in length. The sale of such turtles has been banned in the United States by regulation since 1975 because of the public health impact of turtle-associated salmonellosis. *Salmonella* occur naturally in turtles, and turtles infested with *Salmonella* usually do not appear to be sick. Experts estimate that the regulation, enforced by FDA in cooperation with State and local health jurisdictions, has prevented about 100,000 cases of salmonellosis per year. However, there has been an increase in the sale of small turtles in recent years.

FDA amended the turtle regulation this year to reflect a change in responsibility for administration from FDA's Center for Food Safety and Applied Nutrition to CVM. This action was taken to enable the Agency to more effectively administer the provisions of the regulation. In response to the increase in reports of illegal sales, CVM conducted a public education program, which included placing several educational materials on the CVM web page.

FDA processes requests under an interim final rule to move certain species of animals, such as prairie dogs (USDA photograph)

Monkey Pox

During FY 2005, we processed 153 requests for permission to transport animals under an interim final rule adopted by FDA and CDC in response to an outbreak of monkeypox. The rule requires anyone wishing to move prairie dogs, or six species of African rodents, to obtain permission from FDA prior to transporting these animals. Most of the FY 2005 requests involved the shipment of wild prairie dogs, although we have also dealt with the movement of prairie dogs from one zoo to another, as well as animals moving to research institutions and for educational purposes.

ENFORCEMENT ACTIONS

We received 89 requests for regulatory actions (Warning Letters, injunctions, and seizures), and processed 76 of the requests in an average time of 45 days.

In April 2002, FDA conducted a regulatory inspection of an Iowa livestock healthcare products business after the U.S. Department of Agriculture found unsafe residues of prescription drugs in slaughtered cattle, and the prescription drugs were traced to the firm. The investigation found that the owner of the firm purchased and dispensed veterinary prescription drugs without veterinarians' prescriptions, in violation of Federal law. In addition, the firm provided false and forged documents to drug suppliers in order to justify its continued purchase of prescription drugs. The corporation also used the services of another veterinarian, who sold prescription drugs through the company without ever seeing the livestock he was prescribing drugs for – another violation of Federal law. The firm's president had previously been convicted of introducing misbranded prescription drugs into interstate commerce, a misdemeanor, and the firm had also pled guilty to one count of mail fraud, a felony.

In December 2004, the firm's president and the firm were sentenced to one year of probation, fined $50,000, ordered to pay $50,000 in restitution to FDA, and forfeited $225,000 to the U.S. government.

SURVEILLANCE REVIEWS

We completed 46 consulting reviews to support regulatory enforcement activities involving unapproved veterinary drugs and devices. These reviews evaluate product safety and effectiveness, and help to establish the Center's regulatory priorities. For example, we identified a toxic substance in an oral dental care product that may cause seizure, coma, and liver failure in dogs. This review prevented marketing of the product for use in animals.

We completed 26 additional consulting reviews, including reviews that assisted in determining the regulatory authority over various animal medicinal products, i.e., whether a product is a drug or device (regulated by FDA), an animal biologic (regulated by USDA), or a pesticide (regulated by EPA). For example, the Center provided critical input regarding the regulatory authority over such products as recombinant DNA vaccines, adjuvants for animal vaccines, dried milk products from hyperimmunized cows, neutrophil immuno-modulating peptides, the pesticide rabon in medicated feed, and contraceptive vaccines.

MEDICALLY NECESSARY VETERINARY PRODUCTS (MNVP)

We conducted medical reviews of several veterinary drug products to determine their MNVP status, and made appropriate recommendations for mitigating drug shortages. (A product is considered to be an MNVP if, for example, it can be used to treat a serious disease for which it is not labeled, and there is no other available source of that drug or an acceptable alternative.) The products involved were Cefa-lak, an intramammary infusion product for lactating dairy cows; Cefa-dri, a dry cow intramammary treatment; Cefa Drops and Cefa Tabs for dogs; Iron Dextran Injection; and Terramycin 200 for catfish.

RECALLS

CVM was involved in a total of 109 recalls, at 35 firms, during FY 2005. (This included 83 feed recalls.) Of the total, 17 were Class I recalls, 23 Class II, and 69 Class III. (Class I recalls involve the highest degree of health hazard.)

We conducted Health Hazard Evaluations for several marketed veterinary drug products, determining their recall classifications and recommending the depth of recall based on the seriousness of the products' potential health hazard to animals and/or humans.

DRUG LISTING

Animal drugs in commercial distribution must be listed by the Agency. To improve the Center's ability to make regulatory decisions about products for which it is responsible, CVM has designed a proactive program for updating the drug list. The program involves mailing annually to each animal drug manufacturer or distributor a printout of the drug products that are listed in the firm's Drug Product Listing, accompanied by instructions to update the list. CVM made its 2005 Drug Listing Verification Program mailing at the end of June. We had received responses from approximately 75 percent of the firms by the end of the fiscal year. The remaining firms will be contacted by phone or by mail. Information from the verification reports will allow us to evaluate actions that might have to be taken to avoid shortages of medically necessary animal drugs, enhance our ability to conduct our regulatory duties, and help us to accurately assess user fees under ADUFA.

LABELING CHANGES

As a result of continued monitoring of approved veterinary drug products, several product labels were revised by incorporating post-approval experience information. We recommended these revisions based on thorough review of the Center's Adverse Drug Experience database and/or published literature relating to specific drug products.

Under Center policy, animal drug sponsors publicized several product labeling changes via "Dear Doctor" letters to veterinary practitioners. In addition, we asked the manufacturers of 14 heartworm preventive products to stop promoting their product for 100 percent effectiveness. We also advised sponsors of four oxytetracycline products to incorporate a labeling contraindication against the use of the products to dust uncapped honey bee brood cells, because such use of these products has caused death of larval bees.

BIORESEARCH MONITORING (BIMO)

Our BIMO staff oversees inspection of nonclinical (Good Laboratory Practice), clinical, and sponsor–monitor regulations, to provide assurance of the integrity of data submitted in support of animal drug applications. The BIMO and Administrative Actions team issued a total of 95 inspection requests during FY 2005. Thirty-eight of the inspections requested during the year were completed by the end of the year. BIMO team members provided final classification for 49 inspection reports in 2005; 19 of these reports were from requests made in 2005. We issued three letters of regulatory significance (noting deficiencies in compliance with regulatory requirements) in FY 2005 as the result of our review of BIMO program inspection reports.

EDUCATIONAL OUTREACH

Materials Contract

During the year, a contractor completed field guides (for investigators) and educational materials (for certain target audiences) on three subjects: 1) proper drug use to avoid harmful residues in food producing animals; 2) extra-label drug use under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), which allows licensed veterinarians to prescribe extralabel uses, under specified conditions, of approved animal and human drugs; and 3) veterinary drug compounding. The target audiences for the outreach materials are animal owners and livestock producers, those involved in marketing food animals, food animal veterinarians, faculty and students in agricultural and veterinary schools, drug sponsors and distributors, and other affected individuals or groups. The next phase of the project will be to work with the Division of Human Resource Development in FDA's Office of Regulatory Affairs to conduct FDA field training on the materials and provide instruction on effective methods for presenting the techniques to regulated industry.

Compounding and AMDUCA Training

In cooperation with the FDA Office of Regulatory Affairs, including several regional and district offices, CVM provided training to compliance officers, program monitors, and investigators at two locations in FY 2005. The well-attended three-day courses covered current FDA policy on compounding animal drugs and compounding pharmacies, as well as in-depth training on AMDUCA. This included providing and explaining our newly developed training and outreach materials on AMDUCA, proper drug use, and residue avoidance.

Enhancing Productivity Through Achievement of Management Goals

THE CHALLENGE

Our challenge is to support actively the reshaping of the Agency's management systems and practices in response to the President's Management Agenda, the Secretary's 500-Day Plan, and the goals of the CVM Strategic Plan ("Back to Basics"). Our Office of Management (OM) must ensure that the Center meets the specific management goals for the fiscal year, as described below.

FY 2005 ACCOMPLISHMENTS

Through leadership of OM, the Center successfully met specific performance goals for 2005, as described in the following significant outcomes and achievements.

IMPLEMENTED RESULTS-ORIENTED MANAGEMENT

The Center worked with the FDA Office of Financial Management (OFM) to ensure that the Animal Drug User Fee Act (ADUFA) funding was planned, efficiently spent, and tracked appropriately, as CVM continues to implement this vital program. CVM continues to be on track to meet the established financial goals, as well. The resources will be used to meet challenging new goals associated with ADUFA.

CVM worked with the Office of the Commissioner to establish long-term outcome goals, short-term action items, and annual targets by participating in business process planning groups. The Center is coordinating input from CVM program offices to complete reports within requested timeframes.

The Center's achievements in meeting ADUFA performance and management goals, described elsewhere in this report, provide an example of results-oriented management. Another example is in the nine-step value measurement process implemented by the CVM Staff College during the year to ensure that its program offerings are in alignment with Center goals and are delivering high-value solutions. The process begins with regular and ongoing interaction with Center leadership and employees, review of Center and Agency Strategic Plans, and a review of senior leadership performance contracts – as related to training and development. The program is not limited to training per se, but also encompasses many elements associated with the strategic management of human capital through a comprehensive competency-based organizational development program. Senior leadership performance contract goals cascade downward to the Staff College with relevant goals being incorporated into employee Performance Evaluation Plans. Through this nine-step value measurement process, the CVM Staff College is able to measure performance against goals and identify its program's specific business impact and/or return on investment. This information is also used for continuous program improvement efforts.

FY 2005 Performance (Management) Goals:

- Implement strategic human capital management by targeting recruitment outreach efforts.
- Complete the FY 2005 Competitive Sourcing Program: Focus on the clerical staff.
- Improve Information Technology (IT) Management by supporting the transformation of how the Agency/Center conducts IT operations and consolidates reporting lines of the IT organization in CVM.
- Create administrative efficiencies and consolidate management functions by reducing administrative positions.
- Continue development, expansion, and integration of the Staff College (continue to expand content of in-house programs).

IMPLEMENTED STRATEGIC HUMAN CAPITAL MANAGEMENT

Diversity Initiatives

CVM works with the Agency's Office of Equal Employment Opportunity and Diversity Management (OEEODM) to provide mandatory EEO and Diversity Management Training Programs for all managers and supervisors. The Center is an active participant in the Agency's new Diversity Council, which was established to serve as an advisory body to the FDA Commissioner, the Agency Management Council, and the Director of OEEODM. In support of achieving diversity, CVM's Center Director authored an article titled "Importance of Diversity at CVM" for the June 2005 OEEODM Newsletter. The Center Director also participated in the first FDA Diversity Summit to further support the Agency and Center efforts in this area.

Hiring Innovations

The CVM Staff College has begun the integration of an automated interview tool that is tied to the CVM Competency Model. This will ensure identification and selection of the best-qualified candidates that are learning agile (can continue to learn and remain current with changing medicine, science and technology) and who possess the necessary technical, team, leadership, and management competencies.

PARTICIPATED IN COMPLETION OF THE FY 2005 COMPETITIVE SOURCING PROGRAM

Responding to the FDA's public-private competition for clerical support services, the FDA's Most Efficient Organization (MEO) in February 2005 won the competition to provide clerical services to the Agency. (MEO is the most efficient organization proposed by FDA to compete with outside sources for clerical services.) CVM played an active role on the Performance Work Statement Team/MEO Team in the effort to ensure that these functions remained in the Agency while working to save money for both the government and the taxpayers. CVM will also participate in the Transition Team that has been organized to establish and implement the business processes involved, as well as the overall MEO management structure.

IMPROVED INFORMATION TECHNOLOGY MANAGEMENT

PV-Works Pilot

PV-Works (Vet) is a commercially available off-the-shelf product that provides an animal health drug safety system designed for both animal and human reactions to veterinary pharmaceuticals. PV-Works (Vet) is a flexible system designed to support pharmacovigilance business processes while addressing regulatory reporting requirements worldwide that will adopt Veterinary International Cooperation on Harmonization (VICH) guidelines and VEdDRA (a list of clinical terms for suspect adverse reactions to veterinary medicines in animals) as these become available. The primary objective of the pilot is to provide CVM's Office of Surveillance and Compliance with a streamlined, fully

automated Adverse Drug Experience (ADE) review process in which reviewers can monitor, track, and assess ADEs, and coordinate, share, and communicate information both internally and externally. Additionally, the pilot also provides a means for CVM to collaborate among experts by enabling them to more constructively and effectively share knowledge. Specifically, the pilot will:

- enable the ADE reviewers to use and manipulate the electronically submitted data for review and assessment purposes;
- automate data validation and incorporation of the business rules; and
- provide CVM with a comprehensive system with full audit trail, escalation procedures, letter generation, and ad hoc reporting capabilities.

FY 2005 accomplishments included:

- The successful installation of PV-Works pilot application and database on a CVM server. New releases of the PV-Works software and configuration changes have been maintained throughout the pilot.
- The creation of test accounts for 10 FDA reviewers to access and test the PV-Works pilot.
- The forwarding to FDA and loading into PV-Works for use by FDA reviewers of over 25 animal adverse event cases input by two animal drug sponsors. Several cases of human exposure input by the two firms were also loaded.

Consolidated Reporting Environment (CRE)

The CRE includes a reporting environment utilizing a robust reporting tool that currently supports the implementation of the full dataset from the Activity Time Reporting (ATR) system, and the relevant reference data from the Submission Tracking and Reporting System (STARS). This flexible reporting environment enables users to access Business Objects and execute defined standard (canned) reports and ad hoc queries. To further enhance the CRE, additional data sets will be added to the data warehouse to support the broad spectrum of reporting including regulatory reporting executed within the Center. Specifically, the CRE:

- provides business users the ability to make informed and efficient decisions by drawing data from diverse sources;
- produces data that are complete, condensed, standardized, and meaningful for the business user; and
- provides a technical architecture that is scaleable and flexible to support the evolving reporting needs of the Center.

FY 2005 accomplishments included:

- implementation of a robust reporting environment supporting the implementation of a dataset with the capability of adding additional source systems;
- release of the CRE production system consisting of data from the ATR system and supporting data from STARS; and
- leveraging of the financial and activity characteristics of data captured in OROS – a data analyzing tool – for reporting needs.

RedDot Content Management System

CVM continued to support and enhance the partnering of employees and Information Technology (IT) by implementing a web content management system. The RedDot content management system maintains a consistent flow of information while permitting designated employees to update content on the CVM website and giving IT personnel the ability to enforce best web practices and content approval processes.

IMPROVED FINANCIAL MANAGEMENT

Implemented the Unified Financial Management System (UFMS) in CVM

In 2005, CVM participated in the Agency's implementation of UFMS, which replaced five accounting systems that had been used previously across the operating divisions in the Agency. The UFMS integrates the Department's financial management structure and provides HHS leaders with a more timely and coordinated view of critical financial management information. The system also facilitates shared services among the agencies and thereby assists management in reducing substantially the cost of providing accounting services throughout HHS. CVM worked with the Agency budget office and the UFMS team to implement the new system within the Center by participating in work groups, and attending meetings and training. CVM's Office of Management also assisted the Center's program offices to ensure that employees requiring access to UFMS/Procurement were properly trained. OM also established a folder on the Center's shared computer drive to make UFMS business procedures and UFMS forms and guidance available to CVM employees. CVM continues to work with the Agency to further refine the system.

IMPLEMENTED NEW EMPLOYEE TRAINING AND DEVELOPMENT PROGRAMS

Growth of CVM Knowledge Center

The Center continued to develop the CVM Staff College that we established in FY 2002. Through the state-of-the-art Knowledge Center, the College provides the framework to support the development and delivery of a robust scientific, management, leadership, and team building curriculum based upon researched and established core competencies necessary for high performance in specific positions and functional areas.

Accreditation of Program Offerings

CVM attracts, employs, and retains a highly educated workforce, with more than 90% of its employees holding advanced scientific, academic, and/or medical degrees. Although these credentials are important, CVM also places significant emphasis on a workforce that is "learning agile" so that CVM will continue to carry out its mission successfully. Consistent with this, some disciplines require continuing education credits to maintain professional standing. During FY 2005, the Staff College obtained accreditation through the Maryland State Board of Veterinary Medical Examiners for its Scientific Seminar Series titled Antimicrobial Resistance – Human, Poultry, Swine, Bovine, and Disease Modeling. Providing in-house continuing education opportunities is a cost-effective and efficient approach; it also serves as a strong recruitment and retention tool for the Center.

An instructor at CVM's Staff College

Staff College Collaboration on New Curriculum

During the year, our Staff College expanded its offerings through collaboration with local universities and colleges. We achieved this by including visiting professors, as well as experts from industry, as faculty in the Staff College curriculum. The faculty provides cutting-edge information regarding current scientific issues and research progress. More than 45 internal and external scientific experts participated in the development and delivery of courses directly related to the scientific/regulatory mission of the Center. In addition, the Staff College, through collaboration with the Center for Drug Evaluation and Research, was also able to share intercenter training opportunities.

CVM's Staff College computer lab

New Course Offerings.....

During FY 2005, the Staff College enhanced learning activities and educational opportunities by providing seminar series and courses presenting information on new and emerging scientific issues. These opportunities are intended to meet the management goal of strengthening the employees' ability to make required scientific decisions. In addition to ongoing courses, we introduced two new series:

New Reviewer Training. This course is designed to achieve the management goal of a more enhanced and predictable drug review performance. It is offered to current new animal drug reviewers, as well as newly hired reviewers. The program aims to reduce the learning curve of new reviewers by 6 to 12 months, from the current estimated 18-month timeframe.

Drug Manufacturing Series. This series was implemented to enhance Center employees' understanding and application of the drug review process.

Leveraging Productivity Through Partnerships

THE CHALLENGE

Budget tightening and other factors have prompted FDA and CVM continuously to seek out partnering opportunities to maximize the use of our resources. Our success in promoting and protecting the public health depends in large part not only on active involvement by our stakeholders, but also partnerships with those whose goals align with ours.

FY 2005 ACCOMPLISHMENTS

We continued work under a number of partnering arrangements during the year. These mutual-benefit arrangements have influenced CVM policies and practices, and have enhanced our research and epidemiological efforts. They are in line with the FDA Strategic Plan priority to ensure effective communication and working relationships with key external stakeholders.

We have highlighted a number of partnership agreements and informal arrangements in this report. Examples include:

- Collaborative effort with USDA and CDC in the National Antimicrobial Resistance Monitoring System. CVM has an agreement with USDA's Agricultural Research Service for the purpose of monitoring animal origin *Salmonella*, *E. coli*, *Campylobacter*, and *Enterococcus* isolates to determine the frequency, characteristics, and changes in susceptibility profiles present in the bacterial populations. We also have an agreement with CDC to monitor human *Salmonella*, *E. coli*, *Campylobacter*, and other bacterial isolates to determine the frequency, characteristics, and trends of resistance determinants present in the bacterial populations.
- Collaboration with the Mexican government, to detect resistance in pathogens that may contaminate food imported to the United States and also pose a hazard to U.S. travelers.
- Arrangements with State regulatory agencies to conduct BSE feed rule and medicated feed inspections. State inspectors accomplished more than half of these inspections during FY 2005 (FDA investigators conducted the remaining inspections).
- Cooperation with USDA and a number of universities in the National Research Support Project #7 (NRSP-7). Public Master Files (PMF) created with NRSP-7 support have aided in 25 unique minor species approvals over the years. PMFs are available to support additional approvals, and work is underway in the development of more PMFs. USDA and FDA jointly sponsored the International Workshop on Minor Species in Rockville, MD, in October 2004.
- Collaborative efforts with universities and industry to provide up-to-date information on scientific issues and research progress through courses offered by the CVM Staff College.
- Development of the Animal Feed Safety System through a Working Group that includes representatives from State regulatory agencies and several FDA components in addition to CVM.

- Coordination with other agencies in responding to specific public health threats. An example is the regulation of movement and prairie dogs and certain other rodents to control the spread of monkeypox. In the monkeypox initiative, we interact with numerous Federal, State, and local government agencies, such as CDC, the U.S. Fish & Wildlife Service, USDA's Animal and Plant Health Inspection Service, State wildlife and public health agencies, and county health agencies.

Communicating With Stakeholders

CHALLENGES

To do the best job it can, CVM must communicate with its stakeholders. Animal health companies, veterinarians, and livestock producers must know about new policies and regulations as soon as possible, particularly because this information helps stakeholders comply with the regulations. Consumers, often reached through reporters and TV producers, need to know what steps CVM has taken to protect the food supply and keep our pets safe. CVM must present information to these diverse audiences about programs and initiatives that are sometimes technical, and usually quite complex. CVM is challenged to present scientific information and regulatory changes to these varied audiences in ways that will be fully understood by each of the audiences. When done successfully, proper communications will help ensure that regulations dealing with human and animal health are correctly followed, and that consumers are well informed and capable of understanding the issues.

FY 2005 ACCOMPLISHMENTS

We undertook a broad range of initiatives to provide important information on public health issues, and CVM programs and accomplishments. Among other things, we provided responses to queries from our stakeholders in the pharmaceutical and animal feed industries, Congress, and consumers on a range of issues and concerns regarding veterinary drugs and devices, and animal food products. Our Communications Staff provides leadership in many of the Center's outreach initiatives, but all of our offices also take leadership and play active roles in the Center's effort to communicate with our constituents. The following highlights illustrate the range of Centerwide participation in communications efforts.

SPECIAL INITIATIVES TO RESPOND TO SPECIFIC PUBLIC HEALTH ISSUES

Video on Detection of Nitrofuran Residue in Food Products

Nitrofurans are mutagens and carcinogens, and have been banned for use in food-producing animals in most countries, including the United States and the nations of the European Union (EU). However, in some nations, nitrofurans are commonly used to treat and control bacterial and protozoan infections in poultry, swine, cattle, and other species. The EU recently reported finding nitrofurans in shrimp imported from Southeast Asian countries.

CVM's Office of Research concluded that it would be useful to show an analytical method for detecting nitrofuran residue to other laboratories, such as the FDA Office of Regulatory Affairs and State laboratories. To accomplish this, CVM is producing a video, "Determination and Confirmation of Nitrofuran Residues in Shrimp," and making it available on DVD and videotape. The method provides CVM and other regulatory agencies with a powerful tool for monitoring nitrofuran residues in food products.

Turtle Safety Educational Program

To help improve voluntary compliance with FDA regulations related to new information about illegal sales of small turtles, which carry risk of salmonella infection in humans, we developed informational fliers for parents, regulators, and health educators about such sales. These fliers were posted on the CVM Home Page at http://www.fda.gov/cvm/CVMConsumers.html, and used by FDA Public Affairs Specialists and other FDA field staff to get this message out to the public. FDA's Florida District Office mailed the fliers to retailers in shopping malls and pet stores along with an information letter that the District developed.

Reminder of Prohibition Against Extra-Label Use of Sulfonamides in Lactating Dairy Cattle

From time to time, CVM issues special releases in response to reports of violation of law and regulations the Center administers. An FY 2005 example resulted after CVM received information indicating that sulfonamides, some in combination with trimethoprim, were being prescribed for use in treating conditions in lactating dairy cattle. This treatment is an extra-label use that is prohibited, and is of particular concern because the unapproved use of sulfonamides is one of the most frequent causes of violative residues in food-producing animals. We issued an UPDATE, alerting veterinarians and others of the prohibited use.

PRESS ACTIVITIES RELATED TO PUBLIC HEALTH ISSUES

The Center communicates specific messages to stakeholders by issuing statements directed to members of the press and others. Messages from the Center, typically sent to trade publications, are issued as "CVM UPDATES." These updates provide notification of proposed or adopted regulations, information about proper animal drug use, enforcement actions, and other actions the Center has taken. The Center issued 25 UPDATES during FY 2005. In addition, the Center works with the Commissioner's Office of Public Affairs to develop FDA press releases on topics with a broader consumer interest. CVM and the Office of Public Affairs cooperated during FY 2005 in developing five press statements, covering issues such as BSE and the withdrawal of approval for enrofloxacin.

EXHIBITS AND PUBLICATIONS

Exhibits To Reach Stakeholders

CVM exhibits at various trade shows to provide information to a cross-section of stakeholders. The shows provide an opportunity for CVM to distribute its numerous publications that explain Center programs, highlighting the Center's work in the area of food safety and animal drug use. During FY 2005, we exhibited at seven events, including the World Dairy Expo and the American Veterinary Medical Association annual meeting, drawing approximately 3,000 visitors to our exhibit.

CVM Exhibit booth at an industry trade show

Publications Directed to Stakeholders

CVM has produced a variety of publications, many of which we distribute to various veterinary practitioner and livestock producer groups. These groups in turn pass the publications on to their members. The CVM publications library includes a set of booklets that explain the antimicrobial "Judicious Use Program," developed by veterinarians to help control the development of antimicrobial resistance. One set of booklets explains the program to veterinarians, and another explains it to livestock and poultry producers.

During FY 2005, CVM began distributing a revised and reprinted version of *FDA and the Veterinarian*. This has been a popular booklet, especially with veterinary schools, that explains FDA-administered laws and regulations that pertain to veterinarians. CVM also publishes a newsletter, *FDA Veterinarian*, that highlights the Center's activities and presents an in-depth look at some of the Center's functions. Examples of topics addressed in the *FDA Veterinarian* during FY 2005 included development of regulatory methods to detect animal drug residue, regulations development under the Bioterrorism Act of 2002, and the Animal Feed Safety System.

CVM's Homepage, www.fda.gov/cvm

ANNUAL REPORT

CVM's FY 2004 Annual Report, the second such report, accomplished the goal of presenting information about the Center to our stakeholders and the general public. The purpose of the report is to explain the Center's goals and initiatives, describe the challenges we face, and report our accomplishments during the fiscal year.

CVM WEBSITE

We continued to update and improve the operation of our website, www.fda.gov/cvm, during the year. These improvements included posting several new pages concerning CVM compliance activities; using a Listserve to disseminate our CVM UPDATES; and administering the website with RedDot, a content management system.

STAFFING, SPACE, AND BUDGET

STAFF

Budgeted staffing levels for CVM and CVM-related field activities are in Appendix E.

SPACE

With the passage of the Animal Drug User Fee Act (ADUFA), CVM required new space to house approximately 80 additional personnel over the first three years of ADUFA. To meet this requirement CVM secured 18,156 square feet of office space on the second floor of Metro Park North IV. To facilitate the ADUFA-related growth in ONADE offices in Metro Park North II, CVM consolidated its Office of Surveillance and Compliance (OS&C) into offices in Metro Park North IV. The OS&C consolidation was completed during the spring of 2005.

To better support CVM business processes in both the Office of New Animal Drug Evaluation (ONADE) and OS&C, CVM acquired an additional 3,500 square feet of space in Metro Park IV to house a Satellite Document Control Unit (DCU). Construction of the Satellite DCU began in 2005 and is expected to be completed in early 2006. Work will continue into 2006 on the remaining phases of the multi-phased ADUFA-driven space plan for ONADE offices in Metro Park North II.

We now have offices in Metro Park North II, Metro Park North IV, and Metro Park North V in Rockville, MD, in addition to the Office of Research facilities in Laurel, MD.

BUDGET

Budget details for FY 2005, including the ADUFA-related funding, are in Appendix E.

APPENDIX A

Significant Regulations, Guidances, and Other Documents

REGULATIONS

Proposed Rule - Designation of New Animal Drugs for Minor Uses or Minor Species. Docket No. 2005N-0329. September 27, 2005.

Proposed Rule - Substances Prohibited From Use in Animal Food or Feed. Docket No. 2002N-0273. October 6, 2005.

GUIDANCES

Guidance for Industry #123 - Development of Target Animal Safety and Effectiveness Data to Support Approval of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) for Use in Animals, Draft Guidance. November 8, 2004.

Guidance for Industry #173 - Animal Drug Sponsor Fees Under the Animal Drug User Fee Act (ADUFA). February 7, 2005.

International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH); Final Guidance for Industry on Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (Chronic) Toxicity Testing (VICH GL-37). February 7, 2005.

International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products (VICH); Final Guidance for Industry on Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Establish a Microbiological ADI (VICH GL-36). February 11, 2005.

Guidance for Industry #176 - Specifications: Test Procedures and Acceptance Criteria for New Veterinary Drug Substances and New Medicinal Products: Chemical Substances. (VICH GL-39, Draft Guidance). May 27, 2005.

Guidance for Industry #177 - Specifications: Test Procedures and Acceptance Criteria for New Biotechnological/Biological Veterinary Medicinal Products. (VICH GL-40, Draft Guidance). May 27, 2005.

Guidance for Industry #163 - Dispute Resolution Procedures for Science-Based Decisions on Products Regulated by the Center for Veterinary Medicine. July 19, 2005.

RISK ASSESSMENT

Notice of Availability - Draft Risk Assessment of Streptogramin Resistance in *Enterococcus faecium* Attributable to the Use of Streptogramins in Animals. Docket No. 2004N-0479. November 24, 2004.

COMPLIANCE PROGRAM

Illegal Residues in Meat, Poultry, Seafood and Other Animal Derived Foods, Compliance Program 7371.006. Revised August 1, 2005.

OTHER DOCUMENTS

Establishment of Animal Drug User Fee Rates and Payment Procedures for Fiscal Year 2006. August 1, 2005.

APPENDIX B

Significant FY 2005 New Animal Drug Approvals

ORIGINAL APPROVALS

REBALANCE (pyrimethamine and sulfadiazine)
An antiprotozoal product indicated for the treatment of horses with equine protozoal myeloencephalitis (EPM) caused by *Sarcocystis neurona*.

TRIBUTAME (chloroquine phosphate, embutramide, lidocaine)
A euthanasia product for dogs.

CYDECTIN Injectable Solution for Beef and Nonlactating Dairy Cattle (moxidectin)
For the treatment and control of various internal and external parasites in beef and nonlactating dairy cattle.

DRAXXIN Injectable Solution (tulathromycin)
For 1) treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica*, *Pasteurella multocida*, and *Histophilus somni* and for the control of respiratory disease in cattle at high risk of developing BRD associated with *M. haemolytica*, *P. multocida*, and *H. somni*; and 2) treatment of swine respiratory disease (SRD) associated with *Actinobacillus pleuropneumoniae*, *P. multocida*, *Bordetella bronchiseptica*, and *Haemophilus parasuis*.

SPECTRAMAST LC Sterile Suspension (ceftiofur hydrochloride, 125 mg/mL)
For the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative staphylococci, *Streptococcus dysgalactiae*, and *Escherichia coli*.

SPECTRAMAST DC Sterile Suspension (ceftiofur hydrochloride, 500 mg/mL)
For the treatment of subclinical mastitis in dairy cattle at the time of dry off associated with *Staphylococcus aureus*, *Streptococcus dysgalactiae*, and *Streptococcus uberis*.

SUPPLEMENTAL APPROVALS

RUMENSIN (monensin)
This approval is the first in dairy cows for the claim "increased milk production efficiency (production of marketable solids-corrected milk production per unit of feed intake)." This approval represents a novel and significant production management tool for dairy producers and has a positive impact on modern dairy production practices.

METACAM (meloxicam)
This Non-Steroidal Anti-Inflammatory Drug is approved as a supplement to add the indication for the control of post-operative pain and inflammation associated with orthopedic surgery, ovariohysterectomy, and castration in cats.

Pyrantel Pamoate Paste (pyrantel pamoate)

This anthelmintic is approved as a supplement to add a new dosage and indication for the removal and control of tapeworms (*Anoplocephala perfoliata*) in horses.

TERRAMYCIN-343 (oxytetracycline HCl) Soluble Powder and OXYTETRACYCLINE HCL SOLUBLE POWDER-343 (oxytetracycline hydrochloride)

For the immersion marking of the skeletal tissues of finfish fry and fingerlings. These supplemental NADAs (new animal drug application) relied on publicly available data contained in Public Master File (PMF) 5667, which were compiled under National Research Support Project #7 (NRSP-7), a national agricultural research program for obtaining clearances for use of new drugs in minor animal species and for special uses.

DECTOMAX (doramectin) Pour-On for Cattle

Adds new persistent effect periods of 77 days against *Bovicola (Damalinia) bovis* and 42 days against *Linognathus vituli*.

DECCOX (Decoquinate) plus CHLORMAX (chlortetracycline) Type A Medicated Article and DECCOX (Decoquinate) plus AUREOMYCIN (chlortetracycline) Type A Medicated Article

Animal Drug Availability Act combinations. These approvals revise the Type B and C labeling with the revised decoquinate range of 12.9 to 90.8 g/ton and chlortetracycline range of 500 to 4,000 g/ton in the Type C complete feed and decoquinate range of 90.9 to 535.7 g/ton and chlortetracycline range of 4,000 to 20,000 g/ton in the Type C supplement feed.

APPENDIX C

Awards

CENTER FOR VETERINARY MEDICINE* 2005 HONOR AWARD RECIPIENTS

*In cases in which the award recipients included individuals from CVM and other organizations, only the CVM staff members are mentioned.

FDA COMMISSIONER'S SPECIAL CITATION

Barbara E. Leach

For a career of outstanding dedication to public service, and administrative excellence in support of the Food and Drug Administration's critical programs, policies, and public health mission.

The Animal Drug User Fee (ADUFA) Financial Implementation Working Group

For outstanding leadership in the effective and efficient implementation of the financial business processes necessary to achieve the goals of the Animal Drug User Fee Act.

Karen S. Alder
Stephanie W. Dove
Lowell P. Fried
Anita L. Heinrich
Cynthia A. Hensen
Charise S. Kasser
Jerome J. McDonald, Ph.D.
A. Robert Miller
David R. Newkirk, Ph.D.
Jacquelyn L. Pace
Glenn A. Peterson, Ph.D.
Gail L. Schmerfeld, J.D.
Herman M. Schoenemann, Ph.D.
Roxanne K. Schweitzer
David E. Wardrop, Jr.
Margaret A. Zabriski, Ph.D.

BSE Rapid Test Kit Evaluation Team

For exceptional efforts in the laboratory evaluations of commercial test kits purported to help prevent the spread of BSE through animal feed.

Dorothy E. Farrell
Russell A. Frobish, Ph.D.
Michael J. Myers, Ph.D.
Jewell Washington
Haile F. Yancy, Ph.D.

Bioterrorism Act – Administrative Detention Final Rule Team

(nominated by the Center for Food Safety and Applied Nutrition)

For extraordinary contributions in drafting the final rule to implement the administrative detention provision of the Bioterrorism Act in an expedited timeframe.

William L. Bargo

Bioterrorism Act – Recordkeeping Final Rule Team

(nominated by the Center for Food Safety and Applied Nutrition)

For extraordinary contributions in reviewing public comments and drafting the final rule to implement the establishment and maintenance of records under the Bioterrorism Act provision.

William L. Bargo
Nadine R. Steinberg, J.D.

Clerical Services Competitive Sourcing Initiative Group

(nominated by the Office of the Commissioner)

For commitment to FDA's clerical services through ensuring every aspect of the competitive sourcing process was thoroughly completed.

Beverly J. Cook
Tracey H. Forfa, J.D.
George Graber, Ph.D.
Gwendolyn Jones
William G. Marnane
David R. Newkirk, Ph.D.
CAPT Lynn O. Post, D.V.M.
RADM Linda Tollefson, D.V.M., M.P.H.

FDA Government Accountability Office Liaisons and Special Contacts

(nominated by the Office of the Commissioner)

For sustained superior performance of GAO liaison duties for the Food and Drug Administration.

Michelle L. Mathias
Roxanne K. Schweitzer

FDA/Securities and Exchange Commission Information Sharing Implementation Team

(nominated by the Office of Regulatory Affairs)

For outstanding performance in developing and implementing streamlined procedures for the sharing of FDA's non-public information with the Securities and Exchange Commission.

Gloria J. Dunnavan
Vernon D. Toelle, Ph.D.

Pharmaceutical Current Good Manufacturing Practices (cGMPs) Working Group

(nominated by the Center for Drug Evaluation and Research)

Successfully completing FDA's initiative on product quality regulations, leading to implementation of new scientific and risk-based approaches to pharmaceutical manufacturing and product quality.

William L. Bargo
Dennis M. Bensley, Ph.D.
Jorge F. Christian
H. Gregg Claycamp, Ph.D.
Gloria J. Dunnavan
Raafat M. Fahmy, Ph.D.
Charles W. Gray, Jr., Ph.D.
Norman R. Gregory
Jo W. Gulley
Mai X. Huynh
Mary G. Leadbetter
June Liang, Ph.D.
William G. Marnane
Merton V. Smith, II, Ph.D., J.D.
Vernon D. Toelle, Ph.D.
Katherine P. Weld, Ph.D.
Geoffrey K. Wong

Shanghai 15 Investigative and Support Team
(nominated by the Center for Drug Evaluation and Research)
For outstanding achievement in a landmark case of data fraud that had significant impact on government-owned and -operated active pharmaceutical ingredient manufacturers in China.

Jorge F. Christian

Strategic Action Item Monitoring System (SAIMS) Team
(nominated by the Office of the Commissioner)
For outstanding efforts in developing, implementing, and managing FDA's Strategic Action Plan Monitoring System (SAIMS), used to track the accomplishment of goals contained in FDA's Strategic Action Plan.

Patricia A. Arnwine
David E. Wardrop, Jr.

AWARD OF MERIT

Richard L. Ellis, Ph.D.
For outstanding performance in support of the Office of New Animal Drug Evaluation on international issues of importance to the Center for Veterinary Medicine.

A. Robert Miller
For providing exceptional leadership to critical management initiatives that have significantly accomplished and advanced the mission and goals of the Center and Agency.

FDA SCIENTIFIC ACHIEVEMENT AWARDS

OUTSTANDING INTERCENTER SCIENTIFIC COLLABORATION

Process Analytical Technology (PAT) Team
(nominated by the Center for Drug Evaluation and Research)
For unique collaborative effort among FDA's PAT Team for developing a regulatory framework that supports innovative pharmaceutical development, manufacturing, and quality assurance.

Dennis M. Bensley, Jr., Ph.D.
William L. Bargo
Raafat M. Fahmy, Ph.D.

FDA EXCELLENCE IN REVIEW SCIENCE

Marilyn N. Martinez, Ph.D.
For recognition of innovation, creativity, problem solving, and extraordinary accomplishments in the area of regulatory review science.

OUTSTANDING SERVICE AWARD

Barry H. Hooberman, Ph.D.
For sustained excellence in risk analytical consultation to interdisciplinary scientific teams addressing existing or emerging risks to human and animal health.

Steven M. Fleischer, D.V.M.
For sustained superior performance reviewing new animal drug applications and for significant contributions to Division and Office policy development.

Elizabeth A. Luddy, D.V.M.
For outstanding service developing, implementing, and updating standard administrative procedures for reviewing new animal drug applications in the Division of Therapeutic Drugs for Non-Food Animals.

Ann M. Norris
For outstanding contributions to the development and implementation of major budgetary and administrative programs in the Center for Veterinary Medicine.

Meg Oeller, D.V.M.
For outstanding service to the Agency through significant contributions in the area of minor use and minor species animal drug development.

Roxanne K. Schweitzer
For outstanding contributions in leading and managing the Center for Veterinary Medicine's budget and finance program during a period of significant change.

CVM Members of the VICH Safety Working Group
For exceptional levels of performance and productivity in their roles as Chair (Dr. Mulligan) and Advisor (Dr. Fernandez) to the VICH Safety Working Group.

L. Thomas Mulligan, Ph.D.
Ana Haydee Fernandez, D.V.M.

Joan N. Urban
For an admirable career of sustained, exceptional service to CVM's managers, Deputy Directors, and Directors in delivering vital administrative and executive secretarial support.

Margaret A. Zabriski, Ph.D.
For outstanding contributions to the Center for Veterinary Medicine's information resources management program during a period of significant change.

Substance Registration System Review Board

(nominated by the Center for Drug Evaluation and Research)

For dedication and scientific excellence in compilation of structure drawing and nomenclature guides for the Substance Registration System, a key component of FDA's Structured Product labeling initiative.

Alem Ghiorghis, Ph.D.
William G. Marnane

GROUP RECOGNITION AWARD

CVM Comments Database Working Group

For exceptional performance in the development of the Strategic Initiative Comments Database to promote consistency in the review of CMC sections of animal drug applications.

Kristen L. Anderson, Ph.D.
Dennis M. Bensley, Ph.D.
Xikui Chen, Ph.D.
Bharati R. Dhruva, Ph.D.
LCDR Wei Guo
CDR M. Thomas Hendricks, Jr., Ph.D.
Mai X. Huynh
Kalatu S. Kamara
Mary G. Leadbetter
June Liang, Ph.D.
William G. Marnane
James K. Nitao, Ph.D.
Michael E. Oehlsen, Ph.D.
Yingning F. Wei, Ph.D.
Geoffrey K. Wong

CVM Staff College Team

For superior team performance in furthering the advancement and expansion of the CVM Staff College and the Knowledge Center.

Stanice L. Cooper
Karen C. Pascal
Eve L. Princler
Sherri Stephenson-Washington

NARMS Retail Meat Group

For exemplary performance of group members in planning, organizing, and successfully executing the first FDA NARMS retail meat annual report.

Jason W. Abbott
Sherry L. Ayers
Mary J. Bartholomew, Ph.D.
Peggy J. Carter
Patricia Cullen
Linda L. English
Sharon L. Friedman
Stuart A. Gaines
Althea Glenn
LT Elvira Hall-Robinson, D. V. M.
Susannah Hubert
Joanne M. Kla
Scott S. Komo, Ph.D.
Patrick F. McDermott, Ph.D.
Shawn D. McDermott
Terry A. Proescholdt, D.V.M., Ph.D.
Sadaf Qaiyumi
Michelle D. Talley
Loretta A. Walker, D.V.M.
Robert D. Walker, Ph.D.
David G. White, Ph.D.
Shaohua Zhao, D.V.M., Ph.D.

National Infrastructure Protection Plan Team

For producing CVM's sector-specific portion of the National Infrastructure Protection Plan (NIPP) for the Department of Homeland Security.

Stephanie W. Dove
Charles E. Eastin, D.V.M., Ph.D., M.P.H., DACVPM
Heidi M. Jackson
Shannon T. Jordre
LCDR Ibrahim Kamara
CDR Alfred W. Montgomery, D.V.M.
Thomas J. Moskal, D.V.M.
William D. Price, Ph.D.
Stephen T. Trostle

Bioterrorism Record Access Guidance Workgroup Team

(nominated by the Office of Regulatory Affairs)

For outstanding contributions in producing FDA's guidance for records access authority under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.

Neal Bataller, D.V.M.

FDA Active Directory Migration Team

(nominated by the Office of the Commissioner)

For accomplishing the successful migration of FDA's network to Microsoft's Active Directory while maintaining the highest level of customer service and network integrity.

D. Shawn Matheny

FDA Emergency Operations Network Incident Management System Development Team

(nominated by the Office of the Commissioner)

For outstanding contributions to the successful development of the first electronic network to exchange and relay integrated emergency-related information among FDA offices and external stakeholders.

D. Shawn Matheny

FDA Enterprise Architecture Working Group

(nominated by the Office of the Commissioner)

For driving the development of FDA's Enterprise Architecture across organizational boundaries to present an Agency-wide view of business operations and their associated technologies.

Margaret A. Zabriski, Ph.D.

Food Allergens/MUMs Legislative Team

(nominated by the Office of the Commissioner)

For outstanding performance assisting Congress in developing and enacting legislation which provides FDA with new food allergen labeling authorities and increases new therapies to treat animals.

Richard L. Arkin, J.D.
Mary J. Bartholomew, Ph.D.
Neal Bataller, D.V.M.
Andrew J. Beaulieu, D.V.M.
Dennis M. Bensley, Jr., Ph.D.
Naba K. Das, D.V.M.
Bernadette M. Dunham, D.V.M., Ph.D.
Kevin J. Greenlees, Ph.D.
Harlan J. Howard, Ph.D.
Diane T. McRae, D.V.M.
A. Robert Miller
Dragan Momcilovic, D.V.M., Ph.D., DACT
Meg R. Oeller, D.V.M.
Julia A. Oriani, Ph.D.
Gail L. Schmerfeld, J.D.
Stephen F. Sundlof, D.V.M., Ph.D.
Vernon D. Toelle, Ph.D.
Linda M. Wilmot, D.V.M.

Internet Enforcement and Policy Working Group

(nominated by the Office of Regulatory Affairs)

For exceptional performance in developing and implementing enforcement policy for FDA-regulated products sold on the Internet.

Mark H. Hackman

Mobile Laboratory Development Team

(nominated by the Office of Regulatory Affairs)

For exceptional achievements related to the development of the Chemical and Biological Mobile Laboratory Units and the training of the analyst volunteers.

Marleen M. Wekell, Ph.D.

Nanotechnology Team

(nominated by the Office of the Commissioner)

For outstanding commitment to FDA's responsibility to bring safe and effective nanotechnology-based medical products to the U.S. consumer.

Steven M. Fleischer, D.V.M.

UFMS Federal Team and UFMS Bearing Point Team

(nominated by the Office of the Commissioner)

For outstanding effort and success in implementing Phase I of the new accounting system for FDA, the Unified Financial Management System (UFMS).

Faith Skordinski, Ed.D.

FDA SCIENTIFIC ACHIEVEMENT AWARD (CVM NOMINATIONS)

CVM ANALYTICAL SCIENCE EXCELLENCE AWARD

Campylobacter Working Group

For the development and validation of a standardized broth microdilution antimicrobial susceptibility testing method for the foodborne bacterial pathogen Campylobacter.

Sonya M. Bodeis
Patrick F. McDermott, Ph.D.

CVM OUTSTANDING SUPPORT SCIENTIST AWARD

Karyn D. Howard

For outstanding support in the design and conduct of research programs and initiatives in compliance with GLP regulation requirements at CVM's Office of Research.

CVM OUTSTANDING INTERCENTER SCIENTIFIC COLLABORATION AWARD

Molecular & Microscopic Analysis of Feed for Processed Animal Proteins Training Cadre

For developing and implementing the training course teaching ORA analysts the PCR-based method that will be used to detect prohibited animal materials in animal feed.

Michael J. Myers, Ph.D.
Haile F. Yancy, Ph.D.

LEVERAGING/COLLABORATION AWARD

BSE Import Sampling Team

For exceptional performance in developing a successful strategy to assure needed, imported feed products from BSE at-risk countries are not contaminated.

Neal Bataller, D.V.M.
Gloria J. Dunnavan
Dragan Momcilovic, D.V.M., Ph.D., DACT
Michael J. Myers, Ph.D.

Dioxin in Food Animal Tissue Residue Investigations Team

For exceptional effort in the investigation of elevated dioxin levels found in food animals.

Gloria J. Dunnavan
Jack Geltman
Randal A. Lovell, D.V.M., Ph.D.
Sandra K. Washington
Kim R. Young

Hormone Misuse in Veal Calves Team

For exceptional performance in developing and implementing a successful enforcement strategy to eliminate the misuse of hormone implants in veal calves.

Andrew J. Beaulieu, D.V.M.
Catherine P. Beck
Daniel A. Benz, Ph.D.
Deborah A. Cera
Gillian Comyn, D.V.M., M.P.H.
Bernadette M. Dunham, D.V.M., Ph.D.
Gloria J. Dunnavan
William T. Flynn, D.V.M.
Tracey H. Forfa, J.D.
Lynn G. Friedlander, Ph.D.
Linda A. Grassie
Harlan J. Howard, Ph.D.
Daniel G. McChesney, Ph.D.
Frances M. Pell
Arnel B. Peralta, D.V.M.
Mark M. Robinson, Ph.D., D.V.M.
Patricia A. Ryan
Jon F. Scheid
Mohammad I. Sharar, D.V.M.
Stephen F. Sundlof, D.V.M., Ph.D.
RADM Linda Tollefson, D.V.M., M.P.H.
Steven D. Vaughn, D.V.M.
Reginald Walker

FDA CRADA Liaisons

(nominated by the Center for Biologics Evaluation and Research)

For guiding FDA staff in the proper use of Cooperative Research and Development Agreements that advance the Agency's mission and support its regulation of products.

David B. Batson, Ph.D.

FDA Emergency Preparedness Exercise Group

(nominated by the Office of the Commissioner)

For outstanding participation in the successful completion of the Agency-wide Functional Emergency Exercise.

Neal Bataller, D.V.M.
Deborah A. Cera
Gloria J. Dunnavan
Jack Geltman
Shannon T. Jordre
Randall A. Lovell, D.V.M., Ph.D.
CDR Alfred W. Montgomery, D.V.M.
Kim R. Young

U.S.–Canada–Mexico Trilateral Cooperation Team

(nominated by the Office of the Commissioner)

For outstanding commitment to addressing public health challenges and furthering public health goals across North America.

Daniel G. McChesney, Ph.D.

QUALITY OF WORK LIFE AWARD

OM Quality of Work Life Team

For enhancing the quality of work life for the employees in the Center for Veterinary Medicine and FDA.

Steven R. Bryant
Dawn F. Calhoun
Heidi M. Jackson

L. Thomas Mulligan, Ph.D.

For creating a work environment that encourages creativity, participation, and decision making in the review process that is critical to CVM and ONADE.

CVM DIRECTOR'S HONOR AWARD

David B. Batson, Ph.D.

First place recipient

For exemplary and sustained leadership in extramural research coordination and oversight, leveraging, and technical committee work.

Mark H. Hackman

Second place recipient

For sustained superior performance in handling a variety of complex and high-profile compliance issues.

CVM ADMINISTRATIVE/COMMUNICATIONS EXCELLENCE AWARD

Linda J. Callahan

For exemplary and sustained service in the coordination and delivery of major Agency administrative management programs for the employees of the Center for Veterinary Medicine.

Jon F. Scheid

For outstanding creative effort in producing CVM's Annual Report, which provides our stakeholders with a summary of the Center's activities and accomplishments to protect human and animal health.

CVM SUPPORT STAFF EXCELLENCE AWARD

Sharon L. Ricciardo

For exemplary performance and support to the Generic Animal Drug Team.

Robin M. Stone

For exceptional performance as the Pre-Approval Inspection Manager, support activities for the DMT Quality System, ADUFA-related metrics, and Project Management.

CVM TEAM EXCELLENCE AWARD

Corporate Database Portal Modernization Development and Implementation Team

For extraordinary effort in the modernization of the CVM applications and implementation of these applications in the FDA portal environment and infrastructure within stringent time constraints.

Karen S. Alder
Stephanie W. Dove
Edward H. Hudson
Elaine A. Johanson
D. Shawn Matheny
Kimberly A. Sanders
Michelle D. Talley
Margaret A. Zabriski, Ph.D.

CVM TEAM EXCELLENCE AWARD

CVM PulseNet Team

For exemplary performance in creating and successfully maintaining the CVM PulseNet program and its outstanding contributions to CVM's intramural and extramural research programs, in particular NARMS.

Jason W. Abbott
Sherry L. Ayers
Sharon L. Friedman
Althea Glenn
Sadaf Qaiyumi
Shaohua Zhao, D.V.M., Ph.D.

ONADE cGMP Team

For exceptional performance in the FDA initiative to enhance the quality of veterinary and human pharmaceutical drug products, and to modernize FDA's CMC regulatory programs.

Dennis M. Bensley, Jr., Ph.D.
H. Gregg Claycamp, Ph.D.
Raafat M. Fahmy, Ph.D.
Charles W. Gray, Jr., Ph.D.
Norman R. Gregory
Mai X. Huynh
Mary G. Leadbetter
June Liang, Ph.D.
William G. Marnane
Katherine P. Weld, Ph.D.
Geoffrey K. Wong

The Post-Approval Review Team

For outstanding performance in the pharmacovigilance of marketed veterinary drugs and implementing labeling revisions to further ensure their safety and effectiveness under actual use conditions.

Martine L. Hartogensis, D.V.M.
Christopher Melluso, D.V.M.
Thomas J. Moskal, D.V.M.
Arnel B. Peralta, D.V.M.
Mohammad I. Sharar, D.V.M.

PHS COMMISSIONED CORPS HONOR AWARDS

PHS OUTSTANDING UNIT CITATION AWARD

For extraordinary leadership developing guidance for industry urgently required by CVM to protect human and animal health in evaluating antimicrobial drugs for food-producing animals.

CDR Charlotte Spires, D.V.M.
RADM Linda Tollefson, D.V.M., M.P.H.

PHS ACHIEVEMENT MEDAL

For providing outstanding support to the Agency Campaign Manager during the 2003 Combined Federal Campaign (CFC).

CDR M. Thomas Hendricks, Jr., Ph.D.

CFSAN TEAM AWARD

Codex Task Force Team
(nominated by the Center for Food Safety and Applied Nutrition)
For excellence, diplomacy, and sheer dedication to the missions of both FDA and Codex in protecting consumers and ensuring fair trade on a global scale.

Steven D. Brynes, Ph.D.
Mary C. Carson, Ph.D.
Richard L. Ellis, Ph.D.
Kevin J. Greenlees, Ph.D.
Philip J. Kijak, Ph.D.
Merton V. Smith, II, Ph.D.
Stephen F. Sundlof, D.V.M., Ph.D.
Steven D. Vaughn, D.V.M.

Early Food Safety Evaluation of New Non-Pesticidal Proteins Team
(nominated by the Center for Food Safety and Applied Nutrition)
For developing and publication of a draft guidance document for industry entitled "Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use."

Michaela G. Aleuynse, Ph.D.
Rial A. Christensen, Ph.D.
William D. Price, Ph.D.

COMBINED FEDERAL CAMPAIGN

David D. Wagner, Ph.D.
Combined Federal Campaign Special Service Award
Presented in recognition of outstanding commitment as the Campaign Manager for the Food and Drug Administration's 2004 Combined Federal Campaign.

APPENDIX D

Publications

Note: Names of CVM staff members are in bold type.

Adams, A., M. N. Ton, **M. M. Wekell**, A. MacKenzie, and F. M. Dong. 2005. Survival of *Anisakis simplex* in arrowtooth flounder (*Atheresthes stomia*) during frozen storage. *J. Food Protec*. 68:1441-1446.

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Bischoff, K. M., **D. G. White**, M. Hume, T. J. Poole, and D. J. Nisbet. 2005. The chloramphenicol resistance gene *cmlA* is disseminated on transferable plasmids that confer multiple-drug resistance in swine *Escherichia coli*. *FEMS Microbiology*. 243:285-291.

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McDermott, P. F., S. M. Bodeis-Jones, and R. D. Walker. (In press). Broth microdilution susceptibility testing of *Campylobacter jejuni* and the determination of quality control ranges for fourteen antimicrobial agents. *Journal of Clinical Microbiology*.

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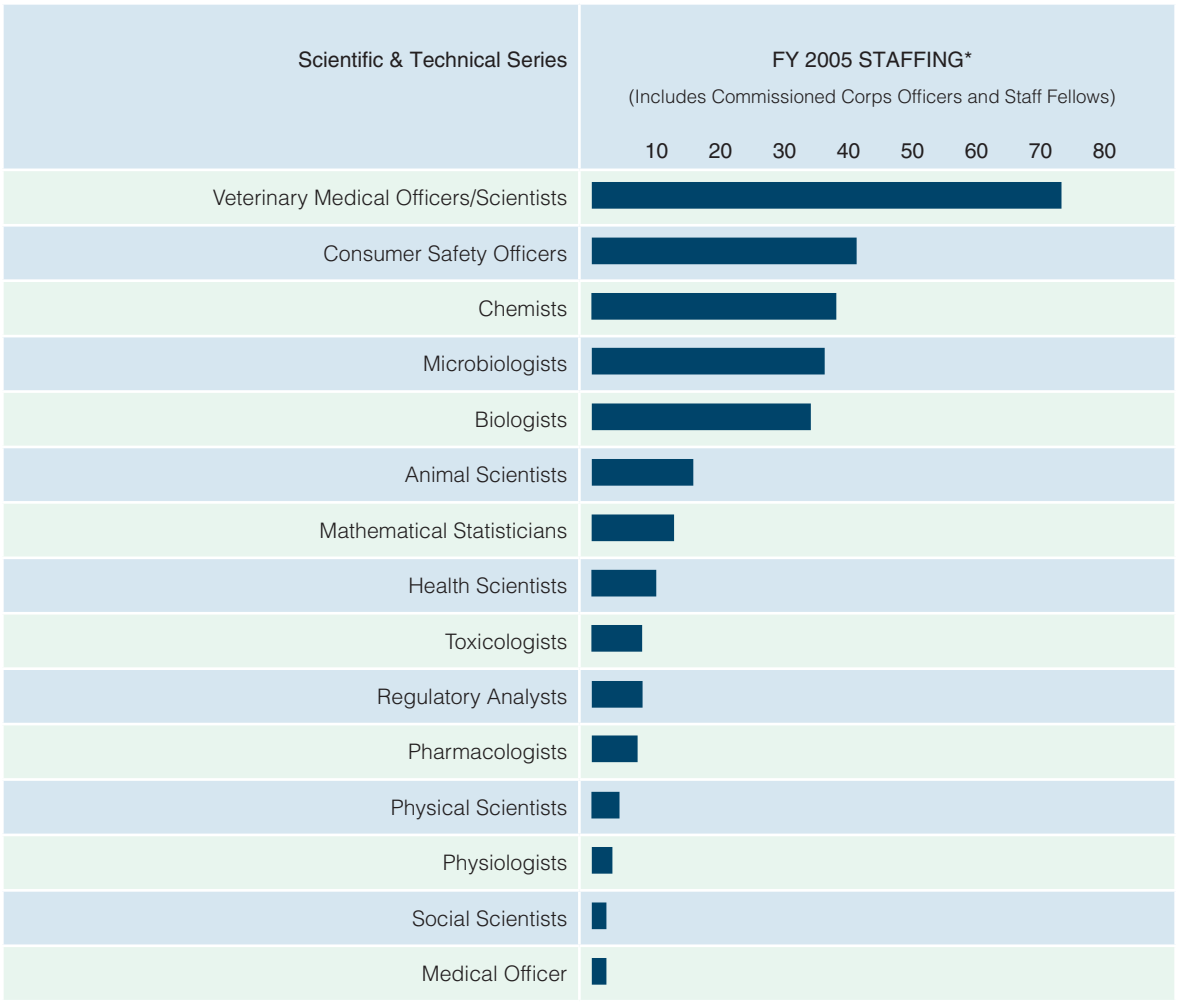
APPENDIX E

Budget

FY 2005 Enacted Budget	Pre-Market	Post-Market	GSA Rent & Rent-Related Activities	FY 2005 Total(s)
Program	$26,005,000	$29,287,000	$12,259,000	$67,551,000
*ADUFA	$ 7,748,000		$359,000	$ 8,107,000
Total Program Level	**$33,753,000**	**$29,287,000**	**$12,618,000**	**$75,658,000**
Note: Estimates for the field are not included in the figures above.				
Field Activities–Animal Drugs & Feeds	$2,013,000	$33,181,000	$4,189,000	$39,383,000

*ADUFA user fee amount does not include money for Other Activities.

Full-Time Equivalent Employees	Pre-Market	Post-Market	FY 2005 Total(s)
Budget Authority (BA)	183	132	315
User Fee (ADUFA)	58		58
Total Program Level	**241**	**132**	**373**
Note: Estimates for the field are not included in the figures above.			
Field Activities–Animal Drugs & Feeds	16	224	240



*Graph does not display 100 percent of CVM Staffing (e.g., excludes consultants and advisory committee members).

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