FDA VETERINARIAN
Center for Veterinary Medicine
March/April 2005 Vol. XX, No. II

FDA Exceeds All ADUFA Goals in First Year of User Fees

The Food and Drug Administration (FDA) exceeded all of its performance goals mandated by the Animal Drug User Fee Act (ADUFA), according to FDA's March 17 report to Congress.

Congress passed ADUFA to make sure that FDA and its Center for Veterinary Medicine (CVM) had the resources necessary for timely drug reviews. Congress passed ADUFA in 2003 and the appropriations act required to permit FDA to implement the act in 2004.

ADUFA mentions the performance goals by reference. FDA and the regulated industry agreed to the goals, and FDA articulated them in a letter to Congress.

Performance is measured by a number of goals, including whether CVM's review of drug applications and submissions are completed by the deadlines that FDA specified in the letter to Congress.

In addition, ADUFA requires FDA to publish an annual performance report. The report CVM released in March, "FY 2004 Performance Report to the Congress for the Animal Drug User Fee Act," covers submissions for FY 2004. (Information about the report and a link directly to it are available at *www.fda.gov/cvm/index/updates/ADUFAFY041.htm.*)

Performance is determined by the total number of FDA review-days from receipt to completion of an application or submission. CVM must complete the review of 90 percent of the eligible applications or submissions within a specified time frame. For example, in 2004, CVM was required to complete a review of 90 percent of New Animal Drug Applications (NADA) within 295 days.

CVM met or exceeded all the review time frames referenced by ADUFA for FY 2004 for applications and submissions that had been acted on as of September 30, 2004. Some applications and submissions received in FY 2004 are pending review and action. They had not reached their deadlines by the end of FY 2004, and are still within ADUFA time frames. FY 2004 performance will be updated in FY 2005 to reflect these pending actions and presented in future reports to Congress.

The time frames to meet the performance goals shorten for each of the five years covered by the current legislation. For instance, the NADA review goal will shorten to 180 days for FY 2008, the last year of the current legislation, from the current 295-day goal.

Another of the goals referenced in ADUFA was for FDA to complete 50 percent of its anticipated hiring for review positions by the end of FY 2005. According to the FY 2004 report, "FDA has made substantial progress in recruiting for its review staff and will meet its goal" of increasing the review staff.

For FY 2005, CVM said, it will offer its reviewers higher levels of professional development so they can stay current with the science. CVM will also offer training of the review staff to improve the knowledge base of the institution.

Still another goal was to complete the review within 24 months of any pending applications or submission received by FDA prior to October 1, 2003. CVM completed review of all 833 pending submissions within 12 months, more than 12 months ahead of the deadline.

CVM issued two guidance documents in FY 2004 to help the animal drug industry understand how the user fee law applied to it. The first one, published in March 2004, explained the user fees and fee waivers. The second, published first as a draft in September 2004, answered most of the industry's questions about user fees. That guidance document was published as final guidance in February 2005.

Definition of action on submission

According to the report, CVM has completed a review of an application or submission when it has made a decision and issued an action letter. A decision does not mean approval. The action letter could mean that the drug

(Continued, next page)

In This Issue

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

CVM Publishes FY 2004 Annual Report

The Center for Veterinary Medicine (CVM) has published its Annual Report for Fiscal Year 2004, placed the report on its website (www.fda.gov/cvm) and sent paper copies to stakeholder groups.

This is the second annual report the Center has issued. Like the first, it describes the organization of the Center and presents the Center's mission, guiding principles, and strategic plan.

Also like last year, the report presents each of the Strategic Goals the management set for CVM, and reports whether the goal was reached. It explains when necessary why the goal was not achieved. For Fiscal Year 2004, the Center identified 44 strategic goals.

A large part of the report is devoted to descriptions of the most important issues. For example, the report discusses the Center's work to implement the Animal Drug User Fee Act, which permits the Food and Drug Administration to collect user fees from the animal drug industry and requires the Center to meet certain performance goals.

In addition, the report talks about implementation of the Minor Use and Minor Species Animal Health Act, which gives the Center new options for reviewing limited-demand drugs.

The report also describes the Center's work to address the risk of antimicrobial resistance, including the work to expand the National Antimicrobial Resistance Monitoring System. And it discusses the work done to control the risks of bovine spongiform encephalopathy (BSE). In addition, the report describes the Center's work in protecting against bioterrorism, reviewing biotechnology issues, and preventing unsafe drug residues in food.

CVM has also conducted extensive research to support work in the areas of review of new animal drug applications, monitoring for antimicrobial resistance, and detection of material prohibited in cattle feed under the BSE feed rule, as the report explains.

In addition, the report lists 10 significant new animal drug approvals and the 40 scientific publications Center staff has been involved with during the year, and dozens of CVM award winners.

The report was published in early May. Interested parties can request a paper copy by contracting the Center for Veterinary Medicine, HFV-3, 7519 Standish Place, Rockville, MD 20855, attn: Jon Scheid.

FDA Exceeds All ADUFA Goals in First Year... *(Continued)*

is approved or an investigational new animal drug application is complete, or it could explain the deficiencies in the application or investigational drug submission.

CVM also has the option under certain circumstances to refuse to file or review an application or submission. If within 30 days CVM reviewers can determine that an application is insufficient on its face or of unacceptable quality for review under current regulations, CVM can refused to file the application. If within 60 days CVM reviewers determine that an investigational new animal drug application is deficient according to requirements specified in the regulations, CVM can refuse to review the submission.

Applications or submissions that CVM decides are not good enough for review are not considered part of the "cohort" of applications that must be reviewed by the established time frames. CVM will report the refusals in its annual report.

Generic approvals unaffected

ADUFA requires that the time frames for the review of Abbreviated New Animal Drug Applications for generic drugs will not increase as a result of ADUFA.

CVM established the baseline for length of time for generic drug review based on the time such reviews took in FY 2001-2003. When compared against the established time frame, review times in 2004 did not increase for completed sentinel submissions, the report said.

CVM reviews generic applications and submissions in a queue that is separate from pioneer applications, supplements, and submissions. CVM has to the extent practical separated staff and functions to provide for the separate queues.

FDA VETERINARIAN

Lester M. Crawford, D.V.M., Ph.D.
Acting Commissioner of Food and Drugs

Stephen F. Sundlof, D.V.M., Ph.D.
Director
Center for Veterinary Medicine

Jon F. Scheid, Editor
Richard L. Arkin, Assistant Editor
Marilyn Broderick, Assistant Editor

Published bi-monthly.
Articles are free of copyright and may be reprinted.
Comments are invited.
Home Page *http://www.fda.gov/cvm/*
Phone (240) 276-9300
FAX (301) 827-4065 or write to:
FDA Veterinarian (HFV-3)
7519 Standish Place
Rockville, MD 20855

Regulatory Action Taken Against Dairy for Drug Residue Problems

The U.S. Attorney's Office in the Eastern District of California has filed a Consent Decree of Permanent Injunction against Alvin L. Souza, an individual doing business as Alvin Souza Dairy, Tulare, CA, that will require the defendant to implement systems to prevent illegal residues of drugs in animals sent to slaughter.

The Consent Decree, filed on April 13, 2005, requires the defendant to implement a means of identifying animals treated with animal drugs and not suitable for slaughter and segregating or quarantining them, keeping medication and treatment records, accounting for drug use, and following label directions when using drugs on the animals.

The Consent Decree was filed in the U.S. District Court for the Eastern District of California.

The U.S. Attorney's office took the case to court after the defendant's animals were found to have numerous illegal drug residues caused by the failure of Mr. Souza and the firm to maintain controls to prevent illegal residues in animals delivered for slaughter.

Although the dairy is not currently selling cattle for slaughter, the firm is engaged in custom heifer-raising operations and bull calf-raising operations. The firm could have more than 5,000 bull and heifer calves at any given time under its control. The business maintains a milking herd of approximately 1,500 animals, and produces approximately 11,000 gallons of milk daily for human consumption.

Leading up to the injunction, investigators reported 13 illegal tissue residues in edible tissues of seven animals sampled by the U.S. Department of Agriculture's Food Safety and Inspection Service between December 1997 and January 2004. Inspectors found illegal residues of antibiotics such as penicillin, gentamicin, neomycin, and sulfadimethoxine. Some of the drug residues were above tolerance levels. For other drugs, though, the Food and Drug Administration (FDA) has not established a tolerance level, so any detectable residue of these drugs is a violation of the regulations.

FDA's San Francisco District conducted the investigation that led to this Consent Decree. CVM's Division of Compliance and FDA's Office of the Chief Counsel, and the United States Department of Justice's Office of Consumer Litigation, were responsible for processing and filing the case.

CVM Officials Call Feedback From AFSS Meeting "Excellent"

More than 200 individuals attended the second public Animal Feed Safety System (AFSS) meeting, held in Omaha, NE, in early April, and offered "excellent" feedback concerning the Center for Veterinary Medicine's (CVM) feed safety work, according to a CVM official.

Dr. George Graber, deputy director of CVM's Office of Surveillance and Compliance, said his AFSS team will need some time to sort through all the information received during the meeting.

In addition, he said, most of those attending appreciated the fact that the meeting was held in the Midwest. The first AFSS meeting was held in a Washington, D.C., suburb. "For the most part, the audience was pleased to have had the opportunity to participate," he said.

The audience included representatives of livestock production groups, the feed industry, consumer groups, State feed control offices, and Food and Drug Administration district offices.

The second meeting was organized similarly to the first; after a general session, the audience was divided into breakout groups that were asked various questions about the AFSS concepts that had been developed.

At the general session, CVM officials explained the draft AFSS Framework, which was released earlier this year. The Framework has four components: the first addressing the safety of feed ingredients; the second identifying the hazards that feed might contain; the third focusing on proper manufacturing, packaging, storing, and distributing feed and feed ingredients; and the fourth about regulatory oversight. (For more information about the Framework, see January/February 2005 *FDA Veterinarian*, page 2.)

CVM officials also presented ideas for a risk-ranking model for determining actual risks posed by hazards that could be in feed.

CVM's AFSS team will review the comments received at the meeting and any other comments submitted later, and then will decide what areas to develop under AFSS.

No additional public meetings are scheduled at this time, but could be scheduled later.

The team expects to complete work on AFSS in 2007.

CVM Official Discusses Career Opportunities with Student Veterinarians at Symposium

by Bernadette Dunham, D.V.M., Ph.D., Deputy Director, Office of New Animal Drug Evaluation

The recent 2005 Student American Veterinary Medical Association (SAVMA) Educational Symposium enabled veterinary students to familiarize themselves with areas of veterinary medicine that are not usually covered in the regular curriculum and to interact with future colleagues, from across the national as well as around the world.

The SAVMA Educational Symposium, hosted by the Texas A&M University College of Veterinary Medicine and Biomedical Sciences, College Station, TX, took place in March. For three days, veterinary students competed in academic and athletic events, attended lectures and wetlabs, and experienced valuable networking opportunities with peers.

The student association was first proposed to students attending the American Veterinary Medical Association meeting in 1966, and it came into being in 1969 as the National Conference of Student Chapters of the AVMA. The name changed to SAVMA in 1972. Currently, the organization has 28 student chapters with more than 8,000 student members.

The 2005 symposium attracted more than 2,000 students, representing veterinary schools not only in the United States, but also in Canada, the West Indies, and Scotland.

SAVMA's invitation to give a lecture on public health issues from a Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) perspective was an opportunity to enlighten many students about the role CVM plays in human and animal health, as well as highlighting the many exciting career opportunities offered by CVM.

The title of my presentation was "Veterinary Medicine: An Umbrella of Opportunities in the Public Health Arena." Most veterinary students have one vision of veterinary medicine and that is the traditional practitioner role. I must confess that I had the same vision when I was a student. However, what students do not often realize is that a degree in veterinary medicine will give them a terrific base from which many career opportunities will present themselves.

Today we see graduates pursuing certification from more than 20 specialty boards. There is also a global demand for all categories of veterinary services. The Pew Health Professions Commission in its report, "Health America: Practitioners for 2005," stated "…there is evidence that there is a potentially significant market for veterinarians and veterinary services, particularly in nontraditional and non-private practice arenas." The report further stated, "Veterinarians are more knowledgeable about the impact of animals and diseases on human health and the role and use of animals in the improvement of health and well-being than any other health professional in most communities. Thus, veterinarians should be more directly available to human health providers for consultation on these subjects."

Career Opportunities for Veterinary Students

There is a wonderful diversity of careers within the professional disciplines of veterinary medicine. Just to name a few, they include:

- Academia
- Animal welfare
- Aquatic medicine
- Biomedical research
- Comparative medicine
- Defense
- Environmental health
- Epidemiology
- Food safety
- Human-animal bond
- Laboratory animal medicine
- Nutrition
- Pathology
- Pharmacology
- Preventive medicine
- Public health
- Regulatory medicine
- Wildlife medicine
- Zoological medicine

CVM's mission

Students are not often familiar with the mission of CVM. As a consumer protection organization, CVM fosters public and animal health by approving safe and effective products for animals and by enforcing applicable provisions of the Federal Food, Drug, and Cosmetic Act. Nor are the students aware of the complexity surrounding the discovery and development of a novel molecule and taking it through to CVM approval as a safe and effective drug that can be legally marketed, promoted, and used. CVM is responsible for ensuring that animal drugs and medicated feeds are safe and effective and that food from treated animals is safe for people to eat.

There are many students and graduate veterinarians who are unaware what a fabulous information resource CVM is regarding FDA-regulated products. That information can be accessed through CVM's web site; CVM Updates; Green Book (which lists all FDA-CVM approved animal drugs); *FDA and the Veterinarian* booklet, (which explains the FDA and CVM regulations that apply to veterinary medicine); National Antimicrobial Resistance Monitoring System (NARMS) brochure and data sets; Freedom of Information (FOI) Summaries for each approved drug; and Adverse Drug Event reporting, just to mention a few.

It was an honor for me to join the SAVMA Career Opportunity Panel and illustrate through personal experiences

(Continued, next page)

Ask CVM

Q: There has been information on the internet about using the drug formalin on goats that could have Caseous Lymphadenitis. Is using that drug in this way legal?

A: This use of formalin is not approved, and FDA has no data supporting the safety or effectiveness of this product for this use.

However, under the provisions of the Animal Medicinal Drug Use Clarification Act, a veterinarian could prescribe an approved formalin product for this use. FDA-approved animal or human drugs may be prescribed for extra-label use providing that certain conditions are met (those in Title 21, Part 530 of the Code of Federal Regulations [*http://www.fda.gov/cvm/index/amducca/530.txt*]). These conditions include establishing a sufficiently long withdrawal time so that food products from the goat do not contain unsafe residues of the drug. This can be done only under the prescription of a licensed veterinarian who is operating with a valid veterinarian-client-patient relationship. The veterinarian must be familiar with the animals involved and be working closely with the animals' caretakers. The veterinarian has the responsibility to determine an adequate withdrawal time supported by appropriate scientific information to prevent residues in the edible tissues.

Because the only approval FDA has for formalin is for immersion of fin fish, we have no data available on the presence of this compound in tissue after injection. Nor do we have data on the safety of this product when injected.

Under law, the only formalin products a veterinarian could use are those that are legally on the market—that have been approved for other uses. CVM has a list of all approved products in the "Greenbook," which is available on CVM's website at (*http://dil.vetmed.vt.edu/NadaSecond/NADA.cfm*). The "Greenbook" shows three approved formalin products, and they are all for topical use in fin fish to control external parasites. They are Formalin-F, by Natchez Animal Supply Co. (NADA 137-687), Paracide-F by Argent Laboratories (NADA 140-831), and Parasite S® by Western Chemical, Inc. (NADA 140-989).

Q: Are the requirements for manufacturing veterinary drugs different than those for human drugs?

A: Veterinary and human pharmaceutical drug product manufacturers must comply with the same current Good Manufacturing Practice requirements. The requirements are listed in 21 CFR Parts 210 and 211. Veterinary and human pharmaceutical drug products also have similar filing requirements. Therefore, veterinary and human pharmaceutical drug products have comparable identity, strength, purity, potency, and quality.

CVM Official Discusses Career Opportunities... *(Continued)*

all of the opportunities that a degree in veterinary medicine affords. The students were most receptive to hearing how our diverse careers evolved.

Participation at the SAVMA Educational Symposium enables us not only to showcase CVM and the exciting career opportunities it can offer, but to enlighten our future veterinarians with the details surrounding the animal drug approval process and their role in providing CVM with feedback on any adverse drug reactions. Together, CVM and the veterinary profession form a partnership that works to ensure the protection of the health of humans and animals.

I also shared with the students one recommendation that they may want to incorporate into their lives and one that has supported me throughout my career; the one golden key to success: Attitude! Having a consistent and positive attitude, along with perseverance, will ensure the best possible outcome. Leadership and professionalism are both dependent on attitude. Attitude is everything!

CVM Personnel Comings and Goings

New Hires

OFFICE OF NEW ANIMAL DRUG EVALUATION

- Scott Fontana, Staff Fellow (Chemist)
- Olutosin Idowu, Staff Fellow (Chemist)

OFFICE OF THE DIRECTOR

- Stephanie Donahoe, Pharmacist

Departures

OFFICE OF THE DIRECTOR

- Joan Urban, Secretary

OFFICE OF SURVEILLANCE AND COMPLIANCE

- Brenda Boateng, Secretary

Food Additive Petition

A Food Additive Petition (FAP 2253) has been filed by Alltech, Inc., proposing to amend the food additive regulations to provide for the safe use of polyurethane polymer coating in ruminant feed. Notice of filing was published January 13, 2005.

A Decade in the Director's Office: An Interview With CVM Director Dr. Stephen F. Sundlof

Part one of a two-part series

Stephen F. Sundlof, D.V.M., Ph.D., has been Director of the Food and Drug Administration's (FDA) Center for Veterinary Medicine (CVM) since 1994. FDA Veterinarian *interviewed Dr. Sundlof about 10 years ago, roughly a year after became CVM Director. We recently sat down with him again to get his views about the Center's progress now that he has a decade's worth of experience at the Center. This first article discusses the Center's policy development work since Dr. Sundlof became CVM's director. In the next issue, he will talk about administrative changes he brought to CVM.*

When asked why you were interested in the position of CVM Director, you cited your involvement with several aspects of animal drug regulation and safety—the National Research Support Program #7 [NRSP-7] and the Veterinary Medicine Advisory Committee (VMAC, as chairman). You also said that, as a result of reviewing 75 volumes of data related to a controversial CVM decision, you had gained new respect for the work of the Center. When Dr. Guest retired, you accepted the urging of some respected people and applied for the job. Now that you have seen the Center inside and out, how have your views changed?

After 11 years as Center Director, my views have changed in a number of respects. But, the fundamental reasons I wanted to come to CVM are the same now as when I applied for the job.

One is that I believe in the mission of CVM and share that commitment to our mission with a cadre of very talented people. Most people who like animals recognize the importance of CVM's role in protecting animal health and assuring the availability of safe and effective products for animals. Being a veterinarian, I have an interest in the health care needs of animals. At CVM I have the opportunity to improve the health of individual animals as well as the health of herds and flocks of animals. That's very rewarding to me.

Another reason I enjoy being CVM Director is the opportunity to contribute to the protection of the public health—that is FDA's mission and also part of CVM's mission.

I am also impressed by the high level of scientific expertise that exists in FDA. FDA is strongly grounded in science. That level of scientific expertise made it attractive for me to leave an academic environment and come to a regulatory environment. Now that I've been here for 11 years I have increased respect for the people who make the Center what it is.

Ten years ago, you said the most important issue facing the Center was drug availability. You said the approval process, with the expected increase in the supply of safe and effective drugs, was the key to food safety. You also wanted to create a regulatory environment that encouraged drug research and development and that allowed economic advantages for small market/small profit drugs so that they would be submitted for review. What progress have you made

(Continued, next page)

A Decade in the Director's Office . . . *(Continued)*

is this area, and how has that affected drug availability? How has the regulatory environment changed?

When I came to CVM, I believed that the way to significantly impact public and animal health was to have a regulatory process that facilitates the approval of important drugs for animal use. In the absence of safe and effective new drugs, veterinarians, animal owners, and producers will use unapproved products that may not work or be safe for the animals or the public. A clear regulatory pathway that would facilitate the approval of safe, effective, and needed animal drugs was needed.

In trying to create that regulatory environment, I've had my share of success, and I've encountered some speed bumps along the way. It hasn't been a smooth and straight path, but, overall, we've made considerable progress in the right direction. I think the destination is a drug review process that is transparent and efficient—and one that facilitates the approval of safe and effective drugs. By facilitating the process, we haven't lowered our standards or regulatory requirements in any way. What we have done whenever possible is to articulate clear guidance to the regulated industry, so they are better able to meet the regulatory requirements for animal drug approvals.

MUMS—the Minor Use and Minor Species Animal Health Act of 2004—provides incentives to animal drug companies for increased investment in research and development to facilitate approval of drugs for minor uses and minor species. This legislation is the result of many years of hard work by Congress, the Center, and a coalition of stakeholder groups. Creating a situation in which drug sponsors were interested in developing drugs for a small market was something we could not do within the regulations that existed prior to 2004. There was a need for fundamental change to the Federal, Food, Drug, and Cosmetic Act in order to create an economically viable pathway to approval for these minor use, minor species drugs. MUMS made those changes. The availability of approved drugs for minor uses and minor species is as relevant today as it was 11 years ago when I was working on what is now the National Research Support Program-7. (NRSP-7 is a U.S. Department of Agriculture program created to foster development of minor use drugs for animal species of agricultural importance. It coordinates with animal producers, drug manufacturers, CVM, the USDA, other government agencies, universities, State Agricultural Experiment Stations, and veterinary schools in the development of minor species drugs.)

Another major milestone in improving the review process was the passage of the Animal Drug User Fee Act (ADUFA) in 2003. What we heard from the animal health industry was that uncertain review times were forcing manufacturers to make business decisions that did not favor the submission of animal drugs to CVM for review for approval. Anything that could be done to provide more predictability to the process would result in additional research and development and lead to more approvals. We discussed this with representatives of the animal drug industry, and they made a compelling business case for providing greater predictability to the industry. They also made it clear that they would be willing to share the financial burden of an enhanced review program, because it would result in a greater return on investment. Their willingness to share in funding an enhanced review process by FDA has been key. In April 2004, the Agency received its first user fee check as part of this initiative.

We are now in an era in which we are increasing staff to review animal drugs, setting clear targets and time frames for the review process, and working with industry to reduce the number of review cycles to approval. FDA and industry would like all applications to receive a "yes" or "no" answer in one cycle, rather than going through multiple submissions and reviews. We are working with the pharmaceutical industry to make sure applications are as clear as possible and to find solutions to problems that have, in the past, led to multiple review cycles. ADUFA is giving us the time and resources to make that happen.

Antimicrobial Resistance

The concern that the use of antimicrobial drugs in food-producing animals can lead to resistance to antimicrobials of importance to human medicine has been a challenge for the Center. How have you handled this challenge?

Shortly before I was selected for this position, a number of articles were published indicating that the "age of antibiotics" was over. The articles stated that fluoroquinolones represented the last new class of antimicrobial drugs for human use, and no new antibiotic drugs were in the development pipeline. Therefore, because fluoroquinolones were the last of the antimicrobial wonder drugs, their effectiveness needed to be protected and preserved at all costs.

(Continued, next page)

A Decade in the Director's Office . . . *(Continued)*

Within a few months of my becoming CVM Director, the Center was faced with the decision of whether or not to approve the first fluoroqinolone for use in a food animal.

We held a joint meeting of the Veterinary Medicine Advisory Committee (VMAC), and the Center for Drug Evaluation and Research's Anti-Infective Drugs Advisory Committee to make recommendations about conditions for the potential approval of fluoroquinolones to treat respiratory disease in poultry. The drug companies testified that flouroquinolones would be used to treat only about 1 percent of poultry. But about 9 billion chickens and approximately 290 million turkeys are produced yearly in the United States, so 1 percent translates to a large number of birds. Fueled by the fear that human medicine would run out of antibiotics and that animal drugs were to blame, there was intense media interest in the meeting. The FDA press office arranged for an interview with a network evening news program. Antimicrobial resistance had been a growing public health concern for more than 20 years, and by the time of the advisory committee meeting, the issue was highly visible, both in the United States and abroad.

The advisory committee generally agreed that there was a need for fluoroquinolone in food-producing animals if certain conditions were met.

The conditions proposed were, first, that the fluoroqinolone be sold by prescription only to veterinarians and not be permitted for over-the-counter sales; second, that it be approved only for therapeutic uses—no sub-therapeutic, growth promotion uses; third, that no extralabel use be allowed; and fourth, that CVM institute a monitoring system to detect emerging antimicrobial resistance and mitigate it in timely fashion.

(The Center has more recently proposed to withdraw approval for the use of fluoroquinolone in poultry. The reason for the decision is that CVM officials detected an increase in resistance in the human pathogen *Campylobacter*. The Notice of Opportunity for Hearing, published in October 2000, said that FDA/CVM "proposed to withdraw approval of the new animal drug application for use the fluoroquinolone enrofloxacin in poultry based on CVM's determination that the use of fluoroquinolones in poultry causes the development of fluoroquinolone-resistant *Campylobacter*, a human pathogen, in poultry; this resistant *Campylobacter* is transferred to humans and is a significant cause of the development of resistant *Campylobacter* infections in humans; and resistant *Campylobacter* infections are a human health hazard. Therefore, CVM is proposing to withdraw the approval of the new animal drug application for use of enrofloxacin in poultry on the grounds that new evidence shows that the product has not been shown to be safe as provided for in the Federal Food, Drug, and Cosmetic Act.")

What has Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern," done for industry?

The development of antimicrobial resistance in drugs of human importance had a dampening effect on the availability of new antimicrobial drugs for food animals. Dealing with this issue has been a challenge for me, for the Center, and for the drug industry. Guidance for Industry #152 laid out a suggested regulatory path drug sponsors can follow to demonstrate the microbial safety of proposed uses of antimicrobials. It uses risk assessment and risk management principles in determining the safety of the antimicrobial drug. Guidance 152 brought stability to the approval requirements for antimicrobial drugs by giving clear guidance to industry on the approval requirements. Now that there is a clear regulatory pathway addressing food safety issues associated with antibiotics, we are seeing a number of new applications for antimicrobial drugs.

BSE

Another challenge you found was BSE. How did you and the Center handle that one?

When I became the director at CVM, BSE was an animal disease with no known effect on human health. While there had been some problems with BSE in the United Kingdom, there had been no occurrences in the United States; and if there had been, it would have been handled by the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS). A year later, I was participating in a teleconference with members of the animal feed industry, cattlemen, APHIS, and others when I learned that the U.K.'s Transmissible Spongiform Encephalopathy Advisory Committee had reported that there might be an association between BSE and Creutzfeldt-Jakob Disease in humans.

And at that moment, the world—and my universe—changed.

All of a sudden, BSE became a huge food safety crisis in Europe. It was later described as a "crisis of

(Continued, next page)

A Decade in the Director's Office . . . *(Continued)*

confidence" in the minds of the European public because they felt that their government representatives had not been forthright and truthful. Political upheavals resulted, including large turnovers in government officials in countries where BSE was present. Millions of cattle were destroyed as a result of the outbreak, and there was great fear in the United States that this disease would penetrate the U.S. cattle herd and lead to human deaths, severe disruption of domestic agriculture, and have devastating effects on our economy.

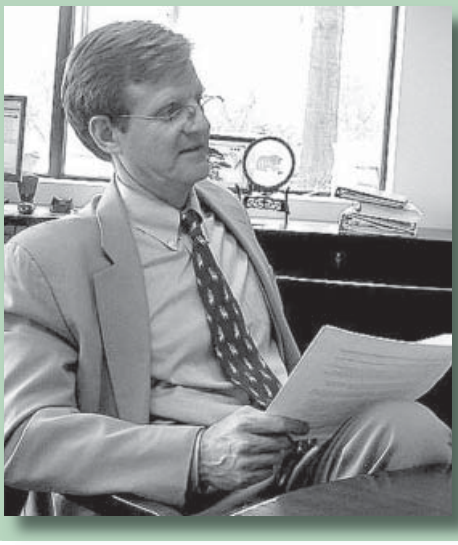
The BSE crisis was one of those moments when the regulated industries and FDA worked together to get things done and manage the crisis. Even so, it was a monumental struggle to actually put the regulations in place that now prohibit the feeding of potentially infective material to cattle and other ruminants. In the end, there was a great coming together of government and industry to make sure that we got it right, and that we were adequately enforcing the regulations.

The BSE crisis turned out to be a great success story. Out of the tumult that surrounded the issue we have a great triumph. The fact that we have high compliance with the regulation—greater than 99 percent for renderers and feed manufacturers—is an indication that there was essentially complete buy-in from the agriculture sector.

Looking back, what effect did the Center's requirement to respond to BSE have on other programs within the Center?

When we issued the 1997 rule prohibiting the feeding of certain cattle materials to ruminants to prevent the establishment and amplification of BSE, we made a major commitment to educate the industry and the public about the new feed regulation before going out to inspect the regulated the industry. We were not provided any additional resources at the time for BSE work, so we took resources away from other areas. Most notably, our tissue residue program, which takes enforcement action against livestock producers that market animals containing drug residues, suffered. But at that point, our highest priority was to make sure that the new BSE feed rule was adequately enforced.

Another impact of the BSE crisis was to divert our focus from the more core functions of CVM—drug approval, feed safety, compliance, and adverse drug reaction/postmarket surveillance. Over the years, we have received increases in the appropriated budget to expand BSE inspection and enforcement and to fund



research to develop test methodologies that help us to enforce the feed rule.

Science

What developments in science have occurred within the past 10 years that have helped CVM the most? What developments are still needed? What scientific developments create the greatest challenges looking ahead?

Genetic engineering is perhaps the most important challenge. Some types of genetically modified animals that were strictly experimental a few years ago are now at the point where they can be produced commercially and have new traits that don't exist in animals that have not been genetically modified. We are seeing transgenic animals that have the potential to grow much faster than non-modified animals, and soon we'll be seeing animals genetically modified to render them immune to certain diseases. We have seen animals that have been genetically modified to produce drugs and biologicals that are harvested from the animals and used to make human vaccines and human drugs. In other words, there is a revolution unfolding before us. A dilemma for us is that the science that has made biotechnology possible has not helped us as regulators in determining whether those animals can be used safely for food.

Cloning is another technology that is at a point where it is ready to be used on a commercial scale to produce livestock and, to some extent, in companion animals. CVM is developing a risk assessment that we hope to release soon on food produced from animal clones.

(Continued, next page)

A Decade in the Director's Office . . . *(Continued)*

Pharmacogenomics is another new technology that will hopefully allow us to make safety and efficacy determinations using surrogate endpoints. This science promises a future in which we may use fewer laboratory animals, or maybe not have to use laboratory animals at all, to make safety and efficacy determinations. This could also help to reduce the cost of drug development and reduce the loss of life of animals presently used in making assessments of drug safety and efficacy.

In addition, the technology used to monitor drug quality as the drugs are being produced is changing. This "real-time" quality testing is starting to take hold in some sectors of the pharmaceutical industry. Testing takes place during production, in real time, and not only at the end-product stage. We think this technology will give us better information than before, and will improve the quality of pharmaceutical manufacturing.

You mentioned earlier that one of the things that attracted you to FDA was the high level of scientific expertise that exists in FDA and how strongly FDA is grounded in science. Does science always dictate CVM's regulatory policy?

One thing I didn't understand prior to taking this job was what it really meant to regulate industries.

I naively thought that as a regulator in a science agency, you evaluate the science, you make your decision, and industry says "OK." Science; decision; move on. I learned that in formulating regulatory policy, science alone is not necessarily enough. Science is not immutable; all science has some inherent uncertainty associated with it, and any decisions that are made based on that science can be challenged because of that inherent uncertainty.

There are a number of factors that influence regulatory policy, especially when risk decisions are being made, including economics and societal values. Because the science is not incontrovertible, and economics and values come into play, the Agency often finds itself in an adversarial role with the regulators, industry, and/or with consumers.

The tension that naturally exists between the regulators and the regulated industry is a lot of what the job is about. I think the industry representatives generally believe that they are right. I don't believe they are being disingenuous for the most part, but they have a vested interest and that helps shapes their beliefs.

The tension that naturally exists between the regulators and the regulated industry is a lot of what the job is about.

In the earlier interview, you said you wanted input from CVM's many stakeholders—the pharmaceutical industry, the livestock industry, feed and pet food industries, companion animal organizations, zoological societies, wildlife conservation organizations, and the veterinary profession. How would you describe the response of these stakeholder groups to the progress of the Center over the past 10 years?

One of the things I probably didn't fully appreciate when I came into this job is how interested CVM stakeholders are in what the Center does. Our stakeholders are generally pretty vocal. We regularly hear from them when they like what we are doing and when they don't. Their comments help shape the policies CVM develops.

Are you saying that response has generally been strong?

Oh yes. I believe that public servants cannot make informed policy without a clear understanding of what the public wants. Of course, the public is not homogeneous. It's made up of individuals who each have a unique perspective about what FDA should do. By listening to a number of diverse perspectives, I believe that our ultimate decision is a much more representative one.

In the earlier interview, you did not discuss CVM's involvement in international work. But since that interview, CVM has become a major supporter and participant in international efforts to harmonize testing protocols and standards for drug approval under Veterinary International Conference on Harmonization (VICH), chairs the Codex Committee on Residues of Veterinary Drugs in Foods, and participated under Codex in developing an international code of animal feeding practices and significant international agreement in the area of antimicrobial resistance. How does this international work relate to your efforts to accomplish your original goals? Can you talk about the importance of these international activities to the Center and the regulated industry?

When I came to CVM, I focused first on CVM's domestic programs, and on our core activities. It soon

(Continued, next page)

A Decade in the Director's Office . . . *(Continued)*

became apparent to me that we live in a global society and that the decisions we make in the United States have ramifications in other countries, and vice versa. This became abundantly clear early in my tenure, when we faced a World Trade Organization (WTO) dispute based on the FDA-approved use of growth hormones in cattle. Because the European Union did not agree with our position that meat from hormone-treated cattle was safe, U.S. cattle were denied access to European markets.

Hormones were just one issue. There were a number of other disputes that never reached the level of formal dispute resolution under the WTO. I learned that even minor areas of disagreement on the regulation of drugs and animal feeds can serve as a focal point for trade disputes. FDA is not a trade promotion agency, but we have a clear responsibility to explain the basis for our regulatory decisions when those decisions come into question as part of a trade dispute.

One way to minimize the likelihood of future trade disputes is to work with other countries to reach consensus on food and drug standards. The international work I have been involved with since coming to CVM has largely been focused on harmonization of veterinary drug residue requirements among the roughly 160 countries that are members of Codex—and to harmonize veterinary drug registration requirements among Japan, the European Union, Canada, Australia, New Zealand, and others that are members of the Veterinary International Conference on Harmonization (VICH).

Looking back over a decade or more, we have made substantial progress in Codex and in VICH, without lowering the high standards of product safety and efficacy that consumers and industry expect from FDA.

Looking back over a decade or more, we have made substantial progress in Codex and in VICH, without lowering the high standards of product safety and efficacy that consumers and industry expect from FDA. We now have a Code of Practice for good animal feeding, which protects consumers from hazards like BSE, dioxins, and contamination with salmonella. Before coming to CVM, I didn't have much of an appreciation for the importance of animal feed as a public health issue. Since then, I have come to understand that animal feeds and human food safety share a number of issues.

Next issue: Changes to CVM's structure to bring about Dr. Sundlof's goals.

Drawing Residue Samples From Live Animals

by Richard L. Arkin

Studies involving tissue-fluid correlation in beef steers hold promise for new test methods that will be able to determine whether drug residues in beef steers are below tolerance levels while the animals are still alive, rather than after they have been slaughtered. These "on-the-hoof" test methodologies could mean less waste and lower production costs.

Scientists at the Center for Veterinary Medicine's (CVM) Office of Research are using liquid chromatography tandem spectrometry (LC/MS/MS) methods to study the distribution of the drugs gentamicin and penicillin in the blood, urine, and kidney tissue of beef steers and relating their findings to the amount of drug residue in animal muscle. The theory is that drug levels in the physiological fluids can be related to drug levels in edible tissues. If so, producers, processors, and regulators could conduct tests on live animals before slaughter to determine if drug levels in edible tissues are violative. If so, the animals could remain alive for longer periods to allow the drugs to clear to nonviolative levels.

If firm relationships between fluid drug levels and drug levels in edible tissues can be established, screening test kits could be developed that would provide a positive response to drug levels in the urine, saliva, or plasma that would correlate to a violative drug concentration in meat. This will allow a rapid decision whether to slaughter

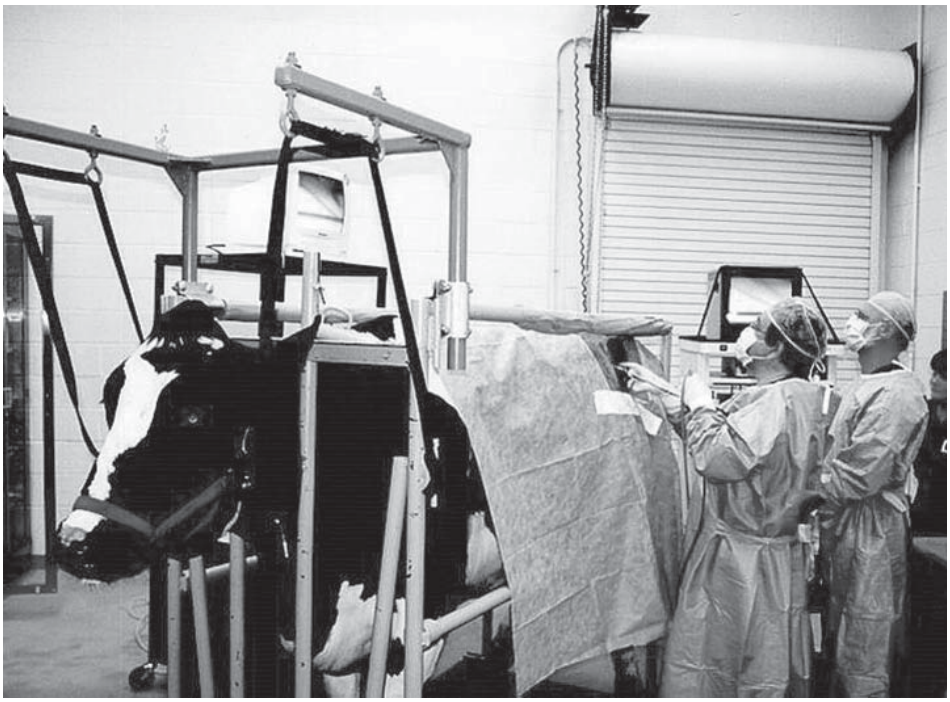
(Continued, next page)

Drawing Residue Samples From Live Animals *(Continued)*

a drug-treated steer or keep it in the feeding pen for an additional period.

CVM scientists have developed laparoscopic techniques to periodically biopsy the kidneys of drug-treated steers. These techniques permit simultaneous monitoring of drug depletion in biological fluids and kidney tissue for the establishment of precise correlations. Methods based on LC/MS/MS have proven to be vital for the measurement of drug concentration in the small samples taken with the laparoscopic procedure: 100 milligrams or less.

Kidney tissue samples are already used in new animal drug research. However, until now, kidney tissue samples have been obtained only from slaughtered animals. As a result, kidney tissue sampling has been limited to a single time point for each animal. In the slaughterhouse, reliance on testing organs such as kidney has meant that a complete animal carcass must be disposed of if the kidney tissues reveal violative drug residues.

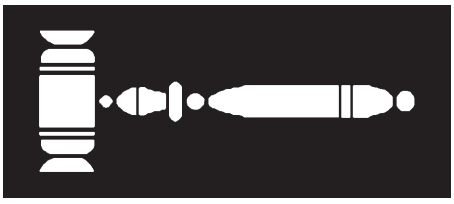


Scientists perform a laparoscopic kidney biopsy of a drug-treated steer.

In contrast, a laparoscopic procedure allows researchers to obtain tissue samples at various time points from the same animal. Successful laparoscopic techniques will reduce the total number of animals required for research and limit or perhaps eliminate the impact of biological variations between individual animals. The data from this research can be used to support live animal testing programs to reduce residue violations and the associated economic loss.

The Office of Research has provided the data and findings from these studies to the U.S. Department of Agriculture's Food Safety and Inspection Service (FSIS). The data will allow the development of on-site screening tests for live animals either for use by FSIS in regulatory testing or by producers and processors in HACCP (Hazard Analysis and Critical Control Point) quality systems. FSIS partially funded this research through an interagency agreement with CVM.

Regulatory Activities



The following individuals and firms received Warning Letters for offering animals for slaughter that contained illegal tissue residues:

- Dennis H. Eldred, Owner, Willet Dairy, LP, Locke, NY
- Sjerp Ysselstein, President, Ysselstein Dairy, Inc., Rock Valley, IA
- Jesse W. Koopman and Anthony Vander Hulst, Partners, West Point Farms, LLC, Wendell, ID

The above violations involved sulfamethazine in a bull calf and a dairy cow, and penicillin and sulfadimethoxine in a culled dairy cow.

A Warning Letter was issued to Dwayne Woody, Owner, W.W. Cattle Company, Poolville, TX, because inspection at his feed manufacturing operation found significant deviations from the requirements sent forth in Title 21, Code of Federal Regulations (CFR), Part 589.2000 – Animal Proteins Prohibited in Ruminant Feed. This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy (BSE). The use of protein derived from mammalian tissues, as defined by 21 CFR 589.2000(a)(1), as an ani-

(Continued, next page)

Regulatory Activities *(Continued)*

mal feed ingredient or in animal feeds must comply with the requirements of 21 CFR 589.2000. The regulations provide that the use of protein derived from mammalian tissues in ruminant feed is prohibited. The definition of "protein derived from mammalian tissues" excludes inspected meat products that have been cooked and offered for human food, and have been further heat processed for use in animal feed. The inspection of the feed manufacturing operation revealed that whole corn dogs, which contain protein derived from mammalian tissues, were sold by the firm for use in ruminant feed are not subjected to further heat processing, causing them to be adulterated feed under Section 402(a)(2)(C)(i) of the Federal Food, Drug and Cosmetic Act (the Act). In addition, because the whole corn dogs are not subject to further heat processing and are thus not exempt from the regulation, they must bear the caution statement, "Do not feed to cattle or other ruminants." The inspection revealed that they do not bear this caution statement, which causes them to be misbranded animal feed under Section 403(a)(1) of the Act.

A Warning Letter was issued to William L. Brown, Owner, Brown Cattle Company, Petrolia, TX, because inspection of his ruminant feeding operation found significant deviations from the requirements set forth in 21 CFR 589.2000. The inspection revealed that prohibited material, as defined by 21 CFR 598.2000(a), was fed to ruminants. The prohibited material consisted of human food processing waste, which is derived from corn dog manufacturing and contains hot dogs and corn dogs. Inspected meat products that have been cooked and offered for human food and further heat processed for animal feed are not prohibited material. However, the human food processing waste used in this operation had not been further heat processed. The failure to further heat process this material causes the feed to be adulterated within the meaning of Section 402(a)(2)(C)(i) of the Act.

A Warning Letter was issued to G. Allen Andreas, Chairman and Chief Executive, Archer Daniels Midland (ADM) Company, Decatur, IL, for significant deviations from Current Good Manufacturing Practice (cGMP) regulations for medicated feeds at the ADM medicated feed mill operation in Des Moines, IA. The deviations include failure to assure that the equipment used in the manufacture of Type A Medicated Articles is operated in a manner that ensures the integrity of the finished product and failure to adequately store incoming bulk drug components in a manner that assures the maintenance of their identity, strength, quality, and purity.

Approvals for January and February 2005

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

SPECTRAMAST LC (ceftiofur hydrochloride) Sterile Suspension filed by Pharmacia & Upjohn Co. (NADA 141-238). The NADA provides for the veterinary prescription use of ceftiofur hydrochloride suspension, by intramammary infusion, for the treatment of clinical mastitis in lactating dairy cattle associated with coagulase-negative *staphylococci*, *Streptococcus dysgalactiae*, and *Escherichia coli*. Notice of approval was published February 28, 2005.

ZIMECTERIN-EZ (ivermectin) 0.6% w/w for Horses filed by Merial, Ltd. (NADA 141-241). The application provides for use of ivermectin meal for the control of roundworms, lungworms, and bots in horses. Notice of approval was published January 11, 2005.

(Continued, next page)

Approvals for January and February 2005 *(Continued)*

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

- RALGRO (zeranol) filed by Schering-Plough Animal Health Corp. (NADA 038-233), a subcutaneous implant/product used in certain classes of cattle or sheep for improved feed efficiency and/or increased rate of weight gain. The supplemental NADA provides for the addition of statements to labeling warning against the use of these products in calves to be processed for veal. Notice of approval was published February 9, 2005.

- RALGRO LA (zeranol) filed by Schering-Plough Animal Health Corp. (NADA 141-192), a subcutaneous implant/product used in certain classes of cattle for increased rate of weight gain. The supplemental NADA provides for the addition of statements to labeling warning against the use of these products in calves to be processed for veal. Notice of approval was published February 9, 2005.

- DECCOX (decoquinate) Type A medicated article filed by Alpharma Inc. (NADA 141-147). The supplemental NADA provides for the use of single-ingredient decoquinate Type A medicated article to make two-way Type B and Type C medicated feeds for cattle at a broader range of concentrations. Notice of approval was published January 14, 2005.

- AUREOMYCIN (chlortetracycline) Type A medicated article filed by Alpharma Inc. (NADA 141-185). The supplemental NADA provides for the use of single-ingredient chlortetracycline Type A medicated article to make two-way Type B and Type C medicated feeds for cattle at a broader range of concentrations. Notice of approval was published January 14, 2005.

CVM has published in the *Federal Register* notice of the approval of these Abbreviated New Animal Drug Approvals (ANADA)

- EUTHANASIA III (pentobarbital sodium and phenytoin sodium) Solution filed by Med-Pharmex, Inc. (ANADA 200-280). The ANADA provides for the use of the product for the humane, painless, and rapid euthanasia of dogs. Med-Pharmex, Inc.'s EUTHANASIA-III Solution is approved as a generic copy of Schering-Plough Animal Health Corp.'s BEUTHANASIA-D Special, approved under NADA 119-807. Notice of approval was published February 24, 2005.

- BIMECTIN (ivermectin) Paste 1.87% filed by Cross Vetpharm Group Ltd. (ANADA 200-326). The ANADA provides for oral use of 1.87% ivermectin paste in horses for the treatment and control of various species of internal parasites or parasitic conditions. Cross Vetpharm Group's BIMECTIN Paste 1.87% is approved as a generic copy of

(Continued, next page)

Approvals for January and February 2005 *(Continued)*

Abbreviated New Animal Drug Applications (Continued)

Merial Limited's EQVALAN Paste, approved under NADA 134-314. Notice of approval was published February 22, 2005.

- Levamisole Hydrochloride Soluble Drench Powder filed by Phoenix Scientific, Inc. (ANADA 200-386). The ANADA provides for the product to be used to make a drench solution for oral administration to cattle and sheep that is effective against various internal parasites. Phoenix Scientific's Levamisole Hydrochloride Soluble Drench Powder is approved as a generic copy of Schering-Plough Animal Health Corp.'s, LEVASOL (levamisole hydrochloride) Soluble Drench Powder, approved under NADA 112-051. Notice of approval was published January 13, 2005.

- LINCOMED (lincomycin hydrochloride) Soluble Powder filed by Cross Vetpharm Group Ltd. (ANADA 200-377). The ANADA provides for oral use of lincomycin soluble powder to make medicated drinking water for administration to swine for the treatment of swine dysentery or to broiler chickens for the control of necrotic enteritis. Cross Vetpharm Group Ltd.'s LINCOMED Soluble Powder is approved as a generic copy of Pharmacia & Upjohn Co.'s LINCOMIX Soluble Powder, approved under NADA 111-636. Notice of approval was published January 11, 2005.

- HEIFERMAX 500 (melengestrol acetate) Liquid Premix filed by Ivy Laboratories (ANADA 200-343). The ANADA provides for use of a liquid Type A medicated article to make dry and liquid Type C medicated feeds for heifers fed in confinement for slaughter and for heifers intended for breeding. Ivy Laboratories' HEIFERMAX 500 Liquid Premix is approved as a generic copy of Pharmacia and Upjohn Co.'s MGA 500 (melengestrol acetate) Liquid Premix, approved under NADA 39-402. Notice of approval was published January 14, 2005.

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

- COMPONENT TE-200 (trenbolone acetate and estradiol) filed by Ivy Laboratories (ANADA 200-346). The supplemental ANADA provides for the addition of heifers to the label of COMPONENT TE-200 (trenbolone acetate and estradiol), a subcutaneous implant, containing 200 milligrams (mg) trenbolone acetate and 20 mg estradiol. The indications are for increased rate of weight gain and improved feed efficiency in steers and heifers fed in confinement for slaughter. Ivy Laboratories' COMPONENT TE-200 is approved as a generic copy of Intervet, Inc.'s REVALOR-200, approved under NADA 140-992. Notice of approval was published February 18, 2005.

- TRIPLEMAX (gentamicin sulfate, U.S.P.; betamethasone valerate, U.S.P.; and clotrimazole, U.S.P. ointment) filed by Phoenix Scientific, Inc. (ANADA 200-287) for the treatment of acute and chronic canine otitis externa. The supplement provides for a new container size, a 20-gram dropper bottle. Notice of approval was published February 18, 2005.

DEPARTMENT OF
HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
HFV-12
Rockville MD 20857

Official Business
Penalty for Private Use $300

PRESORTED STANDARD
POSTAGE AND FEES PAID
TEMPLE HILLS, MD
PERMIT NO. 4004

Use of funds to print the **FDA Veterinarian** has been approved by the Office of Management and Budget.

05-1093