FDA VETERINARIAN

Center for Veterinary Medicine

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FDA RECEIVES NAS/NRC REPORT ON ANIMAL BIOTECHNOLOGY

FDA's Center for Veterinary Medicine (CVM) received a report entitled, "Animal Biotechnology: Science-Based Concerns" from a committee of the National Academy of Science (NAS)/National Research Council (NRC.)

CVM contracted for the report in order to identify food, animal, and environmental safety issues with bioengineered animals and cloning that would be appropriate to address in any science-based regulatory scheme developed for these products. FDA's CVM intends to use the information in the report to help it develop its regulatory approach to animal bioengineering and cloning.

A special NAS/NRC committee—Committee on Defining Science-Based Concerns Associated with Products of Animal Biotechnology—developed the report to identify and prioritize any safety concerns associated with animal bioengineering and cloning. For this report, NAS consulted with experts from both the public and private sector, and it conducted a public meeting late last year to collect additional data and viewpoints from researchers and representatives from public interest groups. CVM funded half the cost of the study. NAS funded the rest.

The committee consulted in the areas of pharmaceuticals; veterinary medicine, aquatic and terrestrial animal physiology; transgenic methods, and chromosome set manipulation; risk assessment; aquaculture biotechnology; cloning; and gene therapy.

The goals of the report are to:

- Develop a consensus listing of concerns in the food safety, animal safety, and environmental safety areas for various animal biotechnology product categories. These categories include, but are not limited to, gene therapy, germ line modifications, knockout technologies, and cloning.

(Continued, next page)

FDA UNVEILS NEW INITIATIVE TO ENHANCE PHARMACEUTICAL GMP'S

The Food and Drug Administration (FDA) recently announced that it is undertaking a significant new initiative to enhance the regulation of pharmaceutical manufacturing and product quality and to bring a 21st century focus to this FDA responsibility.

Photo by Karen Kandra

FDA Deputy Commissioner Dr. Lester M. Crawford

The initiative focuses on FDA's current Good Manufacturing Practice (cGMP) program and will cover veterinary and human drugs, including human biological drug products such as vaccines.

"Americans expect that their medicines will be of the highest quality, and assuring that quality is one of FDA's core missions," said FDA Deputy Commissioner Dr. Lester M. Crawford. "FDA's regulatory and quality control systems for pharmaceutical products have become a gold standard for the world, and we Americans should be proud that the quality of the medicines we have available to us and our animals is second to none. Any system can be

(Continued, next page)

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

. . . REPORT ON ANIMAL BIOTECHNOLOGY (Continued)

- Provide criteria for selection of those concerns considered to be most important that need to be addressed or managed for the various product categories.
- Identify and justify concerns that were considered but not identified as important for certain product categories.

The report is posted on the NAS Home Page at: *http://www.nationalacademies.org/*. Paper copies of the report will be available for purchase from the National Academies Press, *<http://www.nap.edu/>* phone 888-624-8373 (toll-free) or 202-334-3313 (all other calls).

REORGANIZATION WITHIN THE OFFICE OF NEW ANIMAL DRUG EVALUATION

by Joanne Kla

The Office of New Animal Drug Evaluation (ONADE) has just completed the first phase of a two-phase reorganization. The new structure collects all of the scientific review teams that previously reported directly to the Office Director, and incorporates them into a new Scientific Support and Generic Animal Drug Staff, headed by Dr. Gregg Claycamp (HFV-102). The Environmental Assessment

(Continued, next page)

. . . NEW INITIATIVE TO ENHANCE PHARMACEUTICAL GMP'S (Continued)

"Americans expect that their medicines will be of the highest quality, and assuring that quality is one of FDA's core missions," said FDA Deputy Commissioner Dr. Lester M. Crawford.

improved upon, however, and with this risk-based, highly integrative cGMP initiative we intend to do just that. We know we can make even a very good system better."

This initiative is designed to improve public health promotion and protection by focusing on three major goals that will augment FDA's pharmaceutical product quality assurance programs across the board.

The first goal will be to enhance the focus of the agency's cGMP requirements more squarely on potential risks to public health, by providing additional regulatory attention and agency resources on those aspects of manufacturing that pose the greatest potential risk.

The second goal will be to help ensure that FDA's essential work in establishing and enforcing pharmaceutical product quality standards does not impede innovation and the introduction of new manufacturing technologies in the pharmaceutical industry.

The third goal will be enhancing the consistency and predictability of FDA's approach to assuring production quality and safety among the FDA's centers and field components.

FDA cannot accomplish these goals alone. Given the global nature of pharmaceutical production today, FDA fully intends to undertake this initiative in close concert and consultation with its regulatory counterparts internationally. In addition, the success of this initiative is strongly dependent on active participation and input from manufacturing quality control experts from industry, academia, government, and consumer groups, and FDA will be actively soliciting such participation as the initiative progresses.

More than 40 years ago, Congress instructed FDA to require that all drugs be produced according to current good manufacturing practice. This requirement came in response to significant concerns about substandard drug manufacturing practices at that time, and it brought modern quality assurance and control principles to drug manufacturing.

In announcing this cGMP initiative, Dr. Crawford emphasized that it will be overseen by a steering committee that includes representatives from all the affected FDA centers: the Office of Regulatory Affairs, the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and the Office of the Commissioner. He noted in addition that this task will be driven by the latest science and technology and will strengthen the public health protection achieved by FDA's regulation of pharmaceutical manufacturing. He added that FDA remains committed to strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs. He also pointed out that this work may take time—potentially up to two years, or more, for certain aspects of this initiative.

FDA VETERINARIAN

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REORGANIZATION WITHIN ONADE (Continued)

Team, formerly located in the Division of Manufacturing Technologies, is officially moved (and renamed) under the reorganization to become the Environmental Safety Team in the new Scientific Support and Generic Animal Drug Staff. These changes are reflected in Chart A below. With the exception of the movement of the Environmental Safety Team, the Review Divisions in the Office are not directly affected by this reorganization.

Another change to the Scientific Support and Generic Animal Drug Staff is the recent addition of Dr. Larisa Rudenko. Dr. Rudenko joined the Risk Analysis Team as a Senior Advisor for Risk Analysis on July 29, 2002. Dr. Rudenko brings expertise in biotechnology risk analysis to collaborations with the Animal Biotechnology Working Group analyzing potential human, animal, and environmental risks associated with animal cloning and biotechnology, and to the Risk Analysis Team, working on antimicrobial resistance from food animal uses of antimicrobial drugs.

Before coming to CVM, Dr. Rudenko founded Integrative Biostrategies, LLC, a Washington-based firm working at the interface of biological sciences, regulatory affairs, policy and business decisions. Dr. Rudenko has been actively involved in the development of biotechnology risk assessment models beginning with evaluating the risk of antibiotic resistance arising from the use of kanamycin resistance as a selective marker for the Calgene FLAVR SAVR® tomato, developing applications for regulatory approvals for foods derived from transgenic microbes, plants, and animals. She recently served as a risk and scientific consultant to the Pew Initiative on Food and Biotechnology.

Dr. Larisa Rudenko

Dr. Rudenko received her A.B. degree form Bowdoin College and her Ph.D. in Cellular and Molecular Pharmacology from the State University of New York at Stony Brook. She is a Diplomate of the American Board of Toxicology.

When both phases of the reorganization are complete, the Office of New Animal Drug Evaluation (ONADE) will ultimately consist of the current five Divisions reporting to the ONADE Director and two new Staffs located within the Office of the Director. In addition to the Scientific Support and Generic Animal Drug Staff an Administrative and Technical Support Staff will be formed to collect all of the administrative/technical support teams that serve at the Office level under one Staff Director yet to be named. Chart B reflects the ONADE reorganization once it is complete.

Joanne Kla is a Consumer Safety Officer on CVM's Communications Staff.

CHART A

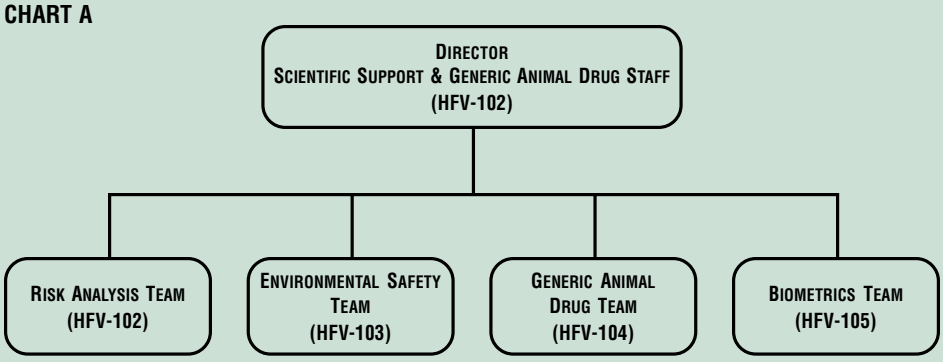
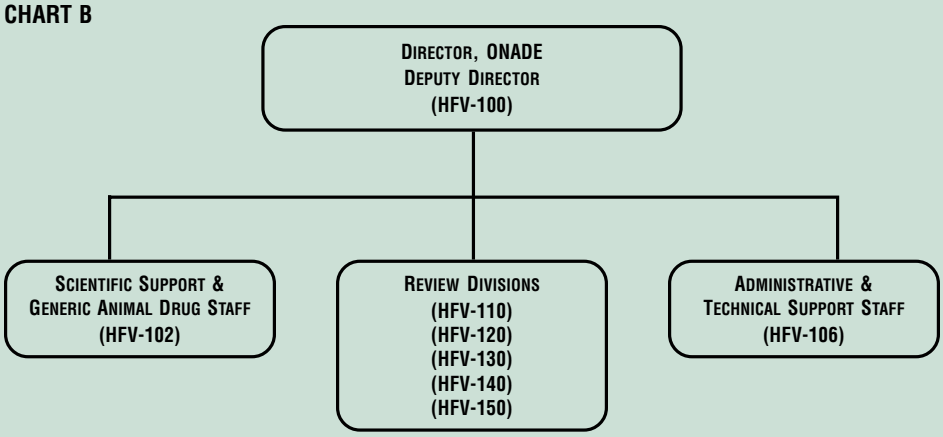


CHART B



CVM STAFF COLLEGE OPEN HOUSE

by Bobbie Giganti

After months of design, development, contracting, procurement, and build out, the CVM STAFF COLLEGE is finally in "residence" with new state-of-the-art facilities.

On Tuesday, July 9, the Staff College held an Open House for Center-wide staff and other invited guests. Program host—Don Peterson, Director, Office of Management, welcomed attendees and introduced the honored guests: Dr. Lester Crawford, Deputy Commissioner/FDA; Dr. Stephen Sundlof, Director, CVM; Mrs. Barbara Leach, Director of Administration; Dr. Faith Williamson, Director of the CVM Staff College; and the Staff College team composed of Stanice Cooper, Bobbie Giganti, Paula Searle, Nancy Scott, Melissa Starinsky, and Sherri Washington.

Photo by Karen Kandra

Dr. Crawford cuts ribbon for CVM Staff College as Dr. Sundlof and Staff College Team watch.

Dr. Crawford was warmly welcomed by staff members-especially those who had worked with him when he served as Director, CVM in the early 1980's. Clearly, Dr. Crawford was glad to be back to visit at CVM and was honored to participate in the CVM Staff College's ribbon-cutting ceremony (a first for Dr. Crawford). In his earlier tenure as CVM Director, Dr. Crawford endorsed the need for developmental opportunities for Center personnel. He was impressed to see and learn how far his early visions had evolved.

In his remarks, Dr. Sundlof emphasized that CVM is embarking upon a new learning and development approach that will benefit CVM employees personally and the organization as a whole. We are a learning organization and the Staff College is the focal point of continuous learning in CVM. Staff will be offered opportunities to develop technical, scientific, management, leadership, and team competencies. Through the use of the Knowledge Center's (KC) Learning Management System (LMS), staff will have the ability to plan their future career path through the use of an automated Individual Development Plan (IDP). The KC currently offers more than 300 online courses; provides employees with instant access to their training records; and provides a wealth of automated information, resources, and tools to help individuals perform more effectively in their current positions or to prepare for a position which they aspire to in the future.

Features of the new facilities include:

- Two training/conference rooms that can be combined to form an area that can accommodate auditorium seating for 50. These rooms can be reconfigured to classroom style seating for 24. These two rooms are equipped with rear room projection, touch panel lecterns with built-in computer presentation equipment, document camera, VCR, videoconferencing, and teleconferencing capabilities.
- Two computer training rooms that can provide hands-on computer training at 15 stations (rooms combined) or 9 stations/6 stations (rooms separated). When set up classroom-style these rooms can accommodate 20-25 people. The computers are recessed into the individual stations so that these rooms can also be used for classroom-style training. These labs are equipped with touch panel lecterns with built-in computer presentation equipment-including SMART Board, instructor computer workstation interaction and monitoring (SnychronEyes), and VCR capabilities. Separate videoconferencing is located for use in one or combined rooms.

For further information on use of these facilities or for Staff College assistance, please e-mail the CVM Staff College at: *CVMStaffCollege@cvm.fda.gov.*

Bobbie Giganti is a Training Specialist currently on detail to the CVM Staff College from Office of Regulatory Affairs' Division of Human Resource Development (ORA-U).

AAFCO ANNUAL MEETING

by Sharon Senesac

The Association of American Feed Control Officials (AAFCO) held its annual meeting in Kansas City, Missouri, August 3-5, 2002. Representatives from 35 States, Canada, U.S. Food and Drug Administration (FDA), U.S. Department of Agriculture (USDA), the press, and industry attended.

International guests from Russia also attended the AAFCO annual meeting this year. The United States Grains Council sponsored their attendance and has been working with their government and industry groups to assist in the development of a regulatory program similar to that of the AAFCO. The Russian contingent was well received.

The AAFCO business session provided the meeting attendees an opportunity to offer comments on the committee reports that had been submitted which recapped the committee activities for the year. Some of the committees had made recommendations of action in their report. The AAFCO membership voted on acceptance or rejection of these recommendations as proposed by the committees. Membership of the newly formed E-Commerce Committee was announced. This committee will deal with issues related to the Internet as well as investigate ways to promote uniformity among the States with regard to various forms that may be used in conducting their regulatory duties.

The Enforcement Strategy for Marketed Ingredients (ESMI) Working Group reviewed its planned strategy to accomplish regulatory control for unapproved feed/pet food ingredients. The ESMI strategy will be implemented later this year with the anticipation of full participation from all the State regulatory control officials. The announcement of the target ingredient, comfrey, for the planned strategy met with little resistance from those in attendance at the meeting. The decision to make comfrey the target ingredient for the planned regulatory action was made after careful consideration and review by CVM of the health and safety concerns surrounding this ingredient.

The Feed Manufacturing Committee (FMC) discussed the draft checklist that has been developed for use in measuring the implementation of the "Guidance/Framework for Best Management Practices for Manufacturing, Packaging and Distributing Animal Feeds and Feed Ingredients." A working group was formed to further revise the checklist with reporting of the working group activities to take place at the January 2003 mid-year meeting.

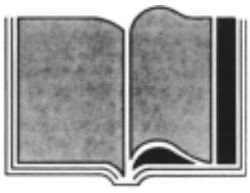
Another topic of discussion during the FMC meeting was process control. Regulators and industry gave their views of AAFCO's desire to proceed in this direction. A small group was assigned the task of developing a definition for process control. The full FMC committee will resume work on this project at the January 2003 mid-year meeting. The FMC also discussed the new language in AAFCO Policy Statement #2, dealing with the use of second-hand bags. A working group was formed to develop a model regulation based on this AAFCO Policy Statement. A proposed draft regulation will be reviewed by the full committee in January.

AAFCO's BSE Task Force met and an update on the current BSE regulations was given by Gloria Dunnavan, Director, Division of Compliance, CVM. She also provided information on the upcoming training session to be held this fall for State and Federal personnel on the agency's new BSE Compliance Program. Dr. Dragan Momcilovic, CVM gave a preview of the BSE methodology workshop that FDA will co-sponsor with AAFCO, to be held in conjunction with the January 2003 mid-year meeting.

The AAFCO Pet Food Committee discussed many issues during its meeting. Among these were the labeling of hairball remedy products, ingredient percentages, requirements for additional guarantees, and the current problems with the labeling of organic pet foods. Dr. Bill Burkholder, a member of the committee from CVM, gave an update on several topics such as changes to the AAFCO Feeding Protocols and other pet food labeling issues. The committee passed a recommendation to add the word "supplement" to PF7(c). If approved by the membership at next year's annual meeting these labels would no longer require a nutritional adequacy statement.

Sharon Senesac is AAFCO's Assistant Secretary-Treasurer.

PUBLICATIONS AVAILABLE



The following new publications are available from the Center for Veterinary Medicine:

- Judicious Use of Antimicrobials for Dairy Producers
- Judicious Use of Antimicrobials for Beef Producers
- National Antimicrobial Resistance Monitoring System – Enteric Bacteria (revised August, 2002)

The following publications are now available in Spanish:

- Guidance for Industry – Animal Proteins Prohibited From Animal Feed; Small Entity Compliance Guide for Renderers (Guidance Document 67)

(Continued, bottom of next page)

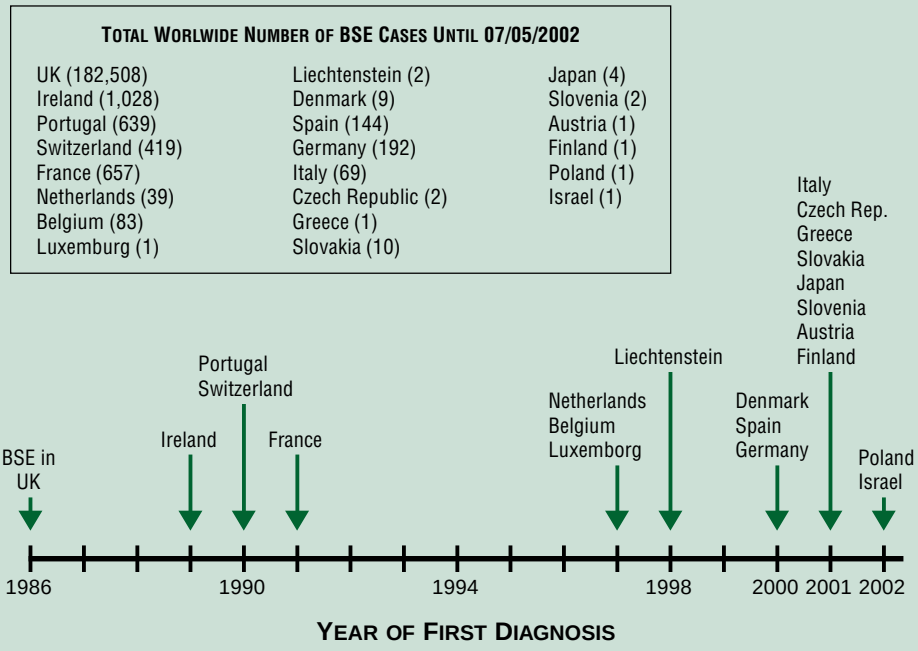
THE SPREAD OF BSE IN SWITZERLAND—EPIDEMIOLOGY AND ONGOING ERADICATION OF A CHALLENGING DISEASE

by Lukas Perler, D.V.M.

Twelve years ago, Switzerland was the first country on the European mainland to diagnose a case of Bovine Spongiform Encephalopathy (BSE) in an indigenous animal. Since then, the spread of this challenging disease has substantially influenced veterinary services and feed control officials. As a result of the ongoing eradication program the number of BSE cases is significantly decreasing and the situation improves gradually.

BSE was first diagnosed in the United Kingdom in 1986. In Switzerland, it was declared a notifiable animal disease in June 1988. The Swiss Federal Veterinary Office subsequently ensured that no further import licenses would be granted for meat and bone meal from Great Britain. In 1989, it started informing veterinarians about this new animal disease—of which there had been no recorded cases in Switzerland previously. Research on diagnostic methods and the epidemiology of BSE was specifically encouraged and from that point special attention was paid to central nervous system disorders in cattle.

FIGURE 1
BSE Cases Worldwide According to the Year of First Diagnosis



PUBLICATIONS AVAILABLE (Continued)

- Guidance for Industry – Animal Proteins Prohibited From Animal Feed; Small Entity Compliance Guide for Protein Blenders, Feed Manufacturers, and Distributors (Guidance Document 68)
- Guidance for Industry – Animal Proteins Prohibited From Animal Feed; Small Entity Compliance Guide for Producers with On-Farm Mixing Operations (Guidance Document 69)
- Guidance for Industry – Animal Proteins Prohibited From Animal Feed; Small Entity Compliance Guide for Producers Without On-Farm Mixing Operations (Guidance Document 70)

To receive copies of any of these publications, contact the Communications Staff at 301-827-3800, or Joanne Kla at *jkla@cvm.fda.gov*.

In November 1990, the first case of BSE on the European mainland that could not be attributed to an animal imported from Great Britain was reported in Switzerland. Material originating from Britain was most probably given new origin labeling and then imported via an indirect route (third countries) to Switzerland. According to the Swiss foreign trade statistics only very small quantities of meat and bone meal were imported directly from Great Britain. Immediately after the first case, measures were taken, the most important being a ban on the use of risk organs for human consumption, implemented on November 8, 1990. On December 1, 1990, a ban on the feeding of mammalian meat and bone meal (MMBM) to ruminants went into effect.

The feed ban on MMBM to ruminants still represents the most important measure to prevent the spread of BSE within the cattle population. In Switzerland, the elimination of all organs that may possibly contain infectivity for BSE (mainly brain and spinal cord from cows) from the rendering process has contributed since May 1996, to further decrease the risk of BSE-transmission. As of January 2001, the feed ban of prohibited material to all farmed animals—total feed ban—has been implemented in Switzerland and the EU member countries.

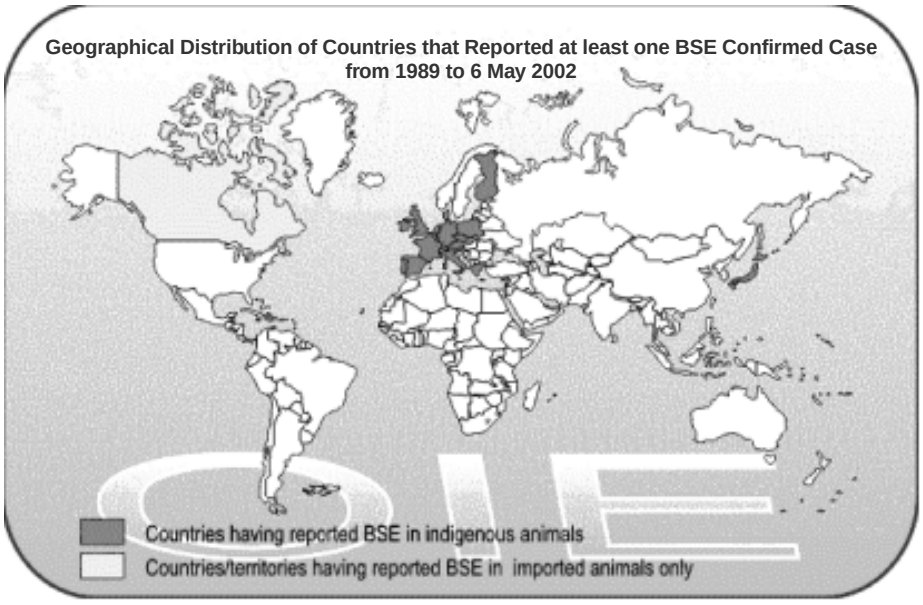
(Continued, next page)

THE SPREAD OF BSE IN SWITZERLAND . . . (CONTINUED)

The average age of the BSE-infected cattle in Switzerland at the time of their death is 5.3 years. The youngest animal was 32 months and the oldest 13 years old. Almost 50% of the affected animals were born after the introduction of the MMBM feed ban (Born after Ban cases). In Switzerland, there is no indication that vertical transmission occurred.

The feed ban on MMBM to ruminants still represents the most important measure to prevent the spread of BSE within the cattle population.

FIGURE 2
Worldwide Distribution of BSE



Source: International Animal Health Organization

Up to 1994 the number of new reports of BSE in Switzerland had almost doubled each year. The peak was reached in 1995 with 68 cases. This number seems comparatively low in comparison to the annual peak of about 36,000 diagnosed cases in the United Kingdom in 1992. In 1996, as a result of the feed ban, a clear trend reversal was seen for the first time in Switzerland, and in 1998 a provisional minimum of 14 cases was recorded. After introduction of active BSE monitoring as part of the surveillance investigation program, the number of cases increased again. In 1999, 25 cows were identified as clinical BSE cases; another 25 infected cows were added to this number on the basis of the specific surveillance program. Since 2001, almost all animals over 30 months are tested for BSE at regular slaughter. Therefore, 42 BSE cases were detected last year. As of the end of July 2002, the number decreased significantly to 12 BSE cases for the ongoing year. Hopefully, this positive trend will continue as a result of the stringent eradication program in Switzerland.

Dr. Perler is a visiting veterinarian from the Federal Veterinary Office of Switzerland. He is a recognized expert on BSE.

TREATING MINOR SPECIES: A MAJOR ANIMAL HEALTH CONCERN

by Linda Bren

This article appeared in the September/October issue of the ***FDA Consumer****.*

Each October, when the mountain wind begins to carry a hint of winter chill, Lyle Johnston of Rocky Ford, CO, loads hundreds of wooden boxes containing a special cargo onto flatbed trucks. He wants those trucks and their valuable cargo—30 million honeybees per truck—to be well down the road and on their way to California before the season's wintry blasts sweep through the Rockies.

The bees are destined to be put to work pollinating the almond fields of California, the source of more than half of the world's almonds. Johnston relies on the almond industry, and the almond industry relies on him and his fellow beekeepers. "Without the bees, the growers get only 300 to 400 pounds of almonds per acre," says Johnston. "With good hives, they get 2,200 to 2,800 pounds per acre."

American farmers rent honeybees to pollinate almonds, apples, melons, and more than a dozen other crops, raising the value of agricultural production by more than $14 billion per year, say entomologists at Cornell University.

(Continued, next page)

TREATING MINOR SPECIES: A MAJOR ANIMAL HEALTH CONCERN (Cont.)

Even so, the honeybee industry is dwindling. "It's a tough game right now," says Johnston, a third-generation beekeeper whose grandfather started the business in 1908. Bees are declining in number, largely because of the destructive efficiency of parasitic mites and American foulbrood, a bacterial disease that infects the young bee larvae and is killing off bee colonies across the nation.

Currently, there are no drugs approved by the Food and Drug Administration to treat the blood-sucking Varroa mites or the suffocating tracheal mites, and the one FDA-approved drug to treat American foulbrood is more than 40 years old. "Consequently, the bacteria have become resistant to treatment across large parts of the United States," says Mark Feldlaufer, Ph.D., research leader at the U.S. Department of Agriculture's (USDA) Bee Research Laboratory in Beltsville, MD.

But through the efforts of the Beltsville Bee Research Lab, the FDA, and a national research program called the USDA Minor Use Animal Drug Program, two more antibiotics to treat foulbrood may soon be available, and studies of a drug to treat Varroa mites will soon begin.

Despite their importance to agriculture, bees are considered a "minor species," and drugs to treat them are included in a category known as "minor use" drugs. There are few FDA-approved drugs available for minor use, but efforts to increase their number are being pursued on two fronts: through new legislation and through research partnerships. These partnerships among government agencies, minor species animal interest groups, universities, public hatcheries, and pharmaceutical companies are producing the data needed to support drug approvals.

A minor species is any animal species other than cattle, horses, pigs, chickens, turkeys, dogs, and cats, which are classified as major species.

Minor species include a wide variety of land animals such as sheep, goats, game birds, deer and elk, bison, emus, ostriches, rabbits, free-ranging wildlife, and zoo animals.

Photo by Keith Weller

Bison are a minor species that produce alternative meats.

They also include birds, ferrets, guinea pigs, and reptiles that are kept as pets. Aquatic animals, such as finfish, turtles, crustaceans, and mollusks, also qualify as minor species.

In addition to treating minor species, minor use drugs can also refer to those used in a major species to control a disease that occurs infrequently or in limited geographic areas. An example of a minor use in a major species is a drug to treat the parasitic infection babesiosis in dairy cattle in tropical regions of the United States.

The MUMS Bill

Only one or two drugs a year, on average, are approved for minor species, says Meg Oeller, D.V.M., the FDA's liaison to the USDA Minor Use Animal Drug Program. "It's a small number compared to the need."

But this number could increase with passage of the Minor Use and Minor Species Animal Health Act, known as the MUMS bill. In response to a congressional mandate under the 1996 Animal Drug Availability Act, the FDA proposed legislative and regulatory changes to improve the availability of drugs for minor uses. Building upon these FDA proposals and with the FDA's technical assistance, a coalition of animal health groups drafted the MUMS bill.

The bill would create a program similar to the FDA's human orphan drug program, which has dramatically increased the availability of drugs to treat rare human diseases. The human program encourages drug companies to seek approval of drugs for rare human diseases and conditions by offering companies help with study design and by giving financial incentives, such as tax relief, grants, and extended periods of marketing exclusivity. Similar incentives might encourage animal drug developers.

The MUMS bill also would provide the FDA some options such as conditional approval when reviewing drugs for minor uses. However, "The bill does not circumvent the need for public health and animal safety standards to be met," says Randy MacMillan, Ph.D., chairman of the MUMS Coalition and president of the National Aquaculture Association. "It would still have the mechanisms in place to address antibiotic resistance concerns, public safety concerns, and environmental concerns."

The MUMS bill was introduced in Congress in 2001 and again in 2002. "We continue to work with . . . congressional people to get the MUMS bill passed as expeditiously as possible," says MacMillan.

Cooperative Research

Drugs to treat minor species used in agriculture are getting a boost from the Minor Use Animal Drug Program.

(Continued, next page)

TREATING MINOR SPECIES: A MAJOR ANIMAL HEALTH CONCERN (Cont.)

Minor Use and Minor Species Animal Health Act
Legislative and Regulatory History

1996	Congress passes Animal Drug Availability Act (ADAA) that requires the FDA to propose ways to improve the availability of drugs for minor uses and minor species
1997	The FDA seeks public comment on documents including "Discussion Draft: Proposals to Increase the Availability of Approved Animal Drugs for Minor Species and Minor Uses"
1998	The FDA concludes Federal statutes should be amended in report "Proposals to Increase the Legal Availability of Animal Drugs for Minor Species and Minor Uses"
1999-2000	MUMS Coalition established; uses FDA proposals and technical assistance to develop draft legislation
2001	The Minor Use and Minor Species Animal Health Act is introduced in Congress, but doesn't pass
2002	The Minor Use and Minor Species Animal Health Act is reintroduced in Congress

Infographic by Renèe Gordon

Source: American Veterinary Medical Association

This USDA program, officially known as National Research Support Project No. 7 (NRSP-7), funds and oversees many of the costly studies required to obtain FDA approval of an animal drug. The results of these studies are made public, and a drug company can then use them without cost to complete the process of applying to the FDA for drug approval. Once approved, the drug can be labeled, marketed, and made available for minor use.

The Minor Use Animal Drug Program works through the cooperation of many organizations. A drug manufacturer agrees to sponsor the drug; state agricultural research services, universities, and veterinary schools conduct studies; animal producers do field testing; and the FDA's Center for Veterinary Medicine (CVM) advises on the requirements needed for drug approval and reviews study results and other data.

Most of the program's efforts involve drugs already approved in a major species. For example, a drug approved for cattle may be studied for its safety and effectiveness in sheep. "With the sponsoring drug company's consent, we can use their toxicology and other data so we don't have to duplicate studies," says Stephen F. Sundlof, D.V.M., Ph.D., director of CVM. "This reduces some of the data requirements and saves a tremendous amount of money."

The program prioritizes and selects projects from requests made by animal producers, veterinarians or researchers. Current funding allows for about 1 in 6 requests to be researched.

Animal Drug Shortages

The continued shortage of minor use drugs not only poses a serious threat to the health of animals—it also may set in motion a chain of events that could adversely affect nearly every American.

First, American farmers could find their livelihoods threatened, since unhealthy animals create significant losses to producers. Second, the American economy could face a worsening trade deficit, since more food animal products would need to be imported to make up for the loss. And third, American consumers could be exposed to a poorer quality of some imported food, since certain animal products originate in countries whose safety and environmental laws may be less stringent than U.S. standards.

So why the shortage of minor use drugs? "There is no economic incentive for pharmaceutical companies to get approval for these drugs since they affect a small population," says Sundlof. "Companies may feel that the size of the market doesn't justify the drug development costs."

Animal drugs must be approved for each species they are intended to treat. Just to add a new species to the label of an

(Continued, next page)

TREATING MINOR SPECIES: A MAJOR ANIMAL HEALTH CONCERN (Cont.)

existing drug costs $2 million to $8 million. To get a brand-new drug approved, it costs a drug company an estimated $20 million and 8 to 10 years of concentrated research efforts.

Focus on Fish

Fish farming, or aquaculture, is one of the fastest growing segments of American farming, says the USDA. Yet to satisfy America's taste for seafood, the United States imports over $9 billion worth of fish each year—more than three times as much as it exports.

"The task for domestic producers is to supply a superior quality product at a reasonable cost," says MacMillan. "What the U.S. aquaculture industry needs is improved health-management systems. We need more vaccines and we need to be able to prevent infectious diseases. In the interim, we need methods to treat sick fish."

The USDA estimates losses of more than $100 million each year, attributable to 50 different fish diseases.

Aquaculture organizations and government agencies are investing heavily in drug research to help ease future losses to industry. The International Association of Fish and Wildlife Agencies, U.S. Fish and Wildlife Service, U.S. Geological Survey, USDA Minor Use Animal Drug Program, and commercial aquaculture operations are among those working in partnership to increase the availability of treatments for fish diseases.

Japan, a major seafood producer, has more than two dozen drugs or combinations of drugs approved for use in its aquaculture industry, according to the American Veterinary Medical Association. The United States has just six drugs approved for use in food fish.

"Water quality in many developing countries is not as good as ours," says Roz Schnick, who helps producer groups and pharmaceutical and chemical companies work together to gain drug approvals. "This creates more stress on the animals, and with stress comes disease so they have to use more drugs," says Schnick. "In the United States, we don't need a lot of drugs—just a basic medicine chest that we are currently attempting to achieve through proper approval procedures."

Schnick reports that through the efforts of Federal and State government agencies and a consortium of aquaculture organizations, the medicine chest will soon fill up—four new aquatic animal drug applications and two supplemental applications are close to being submitted to the FDA for approval.

Additional aquaculture drug research may be expedited through "species grouping." In aquaculture, where there are hundreds of species, it is not practical to test a drug on all of them, says the FDA's Oeller. Researchers are trying to group similar species of fish in order to test drug effectiveness, safety in target animals, and safety in human food. This grouping may yield representative species whose data can be used to support including similar species on the label of a new animal drug.

Fish are not the only animals that can benefit from species grouping research, says Oeller. Other groups may include game birds (pheasants, partridges, quail), deer (white tail, red deer, elk), and ratites (ostriches, emus). "It may be that the research will show that the species are not similar, or are not similar for some classes of drugs," says Oeller. "Learning what is and is not suitable for grouping will be very valuable in making drug approval for minor species more efficient."

Alternative Meat Animals

Although much of its minor species research centers on aquatic animals, the Minor Use Animal Drug Program also is investigating the needs of other animals used in agriculture. Some of this research is motivated by the needs of American farmers seeking healthful alternatives to the traditional red-meat market.

Meats from ostriches, emus, bison, deer, and elk have some nutritional benefit over other red meats, according to a USDA-funded study conducted at the University of Wisconsin-Madison. "These alternative meats, like traditional meat and poultry, are high in protein," says Dennis Buege, Ph.D., lead study researcher. "Their cholesterol content is similar to the other meats and poultry. However, they tend to be lower in fat than beef, pork and dark meat chicken, and higher in iron than beef, pork, and light and dark meat chicken." (See "How Meats Measure Up," page 34.)

The Minor Use Animal Drug Program has conducted research to support the approval of a drug for bison, and several projects are in progress for deer and elk. As yet, there are no drugs approved to treat flightless birds known as ratites, but the program recently has received several requests from this growing industry.

The program is researching treatments for diseases in sheep and goats, also minor species. A number of drugs to treat these animals have been approved, but more are needed, particularly to aid America's declining sheep industry.

Sustaining the Sheep Industry

The U.S. sheep population has been steadily decreasing since the 1940s—from its peak at 56 million in 1942 to less than 7 million in 2002, says the USDA.

The lack of approved drugs for sheep is one factor contributing to the decline, says Oeller. The sheep industry loses about $45 million worth of sheep each year from diseases for which drugs are unavailable.

(Continued, next page)

TREATING MINOR SPECIES: A MAJOR ANIMAL HEALTH CONCERN (Cont.)

How Meats Measure Up

(based upon 3 oz. of cooked, trimmed/skinless servings)

Nutrients	Daily Dietary Rec.[1]	Ostrich[2] (top loin)	Emu (loin)	Venison (loin)	Bison (sirloin)	Elk (rib/loin)	Beef[3] (loin)	Chicken[2] (breast)	Chicken[2] (thigh)	Pork[3] (loin)
Calories (kcal)	1600-2800	132	123	128	146	141	182	140	178	173
Protein (gm)	50	24	25	26	24	26	29	26	22	26
Total Fat (gm)	<65	3.3	2.7	2.0	4.8	3.3	8.6	3.0	9.2	6.6
Saturated Fat (gm)	<20	1.0	0.7	1.0	2.1	1.6	3.3	0.9	2.6	2.3
Cholesterol (mg)	<330	79	75	67	73	64	65	72	81	68
Iron (mg)	8 for males; 18 for females	2.8	4.3	3.5	3.0	3.4	2.1	0.9	1.1	0.7

Infographic by Renée Gordon

(gm=grams, mg=milligrams, kcal=kilocalories)

[1] Based on the U.S. Department of Agriculture (USDA) Recommended Dietary Allowances for a 2,000 calorie diet, and the Institute of Medicine's Dietary Reference Intakes for iron

[2] Ostrich Meat Industry Development Final Reports (1993 and 1996), Texas A&M University

[3] USDA Nutrient Database for Standard Reference

Source: Dennis Buege, Ph.D., University of Wisconsin-Madison, and Julliet Howe, Ph.D., USDA Nutrient Data Laboratory

In addition to disease-treating drugs, American sheep ranchers are lacking another important tool: "the capability to manipulate reproduction," says Oeller. In other countries, such as Australia, sheep ranchers can use progesterone implants to manipulate the reproductive cycle. "This gives them spring and fall breeding of sheep, while we are limited to one breeding season in this country," says Oeller.

In response to the industry's need, the Minor Use Animal Drug Program is currently researching a vaginal progesterone for sheep and goats.

Big Birds

Powell Anderson, D.V.M., splits his time between his veterinary hospital in Dillwyn, Va., and his ostrich ranch next door. An ostrich breeder since 1996, Anderson sees the future of agriculture and the rebirth of small farms in businesses like his. It's a healthy and environmentally sound alternative to some other forms of animal food production, says Anderson, who doesn't use growth hormones or antibiotics in his birds.

Anderson sells the low-fat ostrich meat, which he compares to filet mignon in taste, to local restaurants. He incubates the fertile eggs during mating season and sells them for food in the mating off-season. "You can't taste the difference between scrambled ostrich eggs and chicken eggs," says Anderson, who plans to be eating ostrich eggs for a very long time. "The females lay eggs for 40 years and live to be 70."

With no FDA-approved drugs to treat ostriches, Anderson must rely on his own knowledge of veterinary medicine, an ostrich encyclopedia, and trial and error. Luckily, his birds have been pretty healthy, he says, but when one is sick, it goes down quickly. "You can't tell they're sick until they're almost dead."

Sharyn Felts, owner of one of the largest emu ranches in California, also considers herself blessed that most of her 800 emus have been disease-free. The six-foot tall, 150-pound birds, second in size only to ostriches, are very hardy, she says.

In addition to their meat, the emus are valued for their oil as an emollient used in moisturizers, shampoos and soaps. Their feathers are used by fishermen to tie flies, and their hides serve the leather industry. The dark green emu eggs are prized by artists, who carve or paint them.

Off-Label Use and Medicated Feed

The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 eased the scarcity of animal drugs somewhat by allowing veterinarians to use approved animal and human drugs "extra-label," or "off-label." This means that under certain circumstances, veterinarians can

(Continued, next page)

TREATING MINOR SPECIES: A MAJOR ANIMAL HEALTH CONCERN (Cont.)

use drugs approved for other species, for other diseases and conditions, or at different dosage levels from those listed on the drug label.

This flexibility of drug use may help to ease animal suffering, but the different metabolisms of some species make the effective dosage a guessing game, says Oeller. The benefit of having a drug approved for a specific species is that "you can count on a specific withdrawal time and know the correct dosage," Oeller says.

Although the AMDUCA allows off-label use of drugs, it prohibits off-label use in animal feed. But medicated feed often is the best route of getting a drug into certain animals, such as fish and game birds. Injecting an individual fish with a drug may be feasible for some types of brood stock, says MacMillan. "But such injection is not feasible for a large population of farm-raised aquatic animals such as trout, catfish, tilapia or bait fish."

Bill Mac Farlane, who owns one of the nation's largest pheasant farms, located in Janesville, Wis., says he needs medicated feed for his pheasants and other game birds, particularly to treat coccidia, a deadly parasite that infests the intestines. The alternatives to medicated feed don't work very well, says Mac Farlane. It's not practical to catch each bird and give them a shot every day, nor is adding a drug to the water effective. "They don't like the taste of the medicated water. They drink out of the puddles after a rain instead, so they don't get their medication."

To meet the requirements of the fish and bird industries, the Minor Use Animal Drug Program has shifted much of its focus to the approval of medicated feeds, says Oeller. The program is currently testing several medicated feeds for pheasants to treat bacterial infections and coccidia and other parasites, and Mac Farlane's pheasant farm is participating in the study trials.

Keeping Animals Healthy

Currently, the Minor Use Animal Drug Program is working on more than two dozen projects, and continues to review requests for treatments to keep animals healthy. Among the active projects are drugs to treat diseases in game birds, goats, sheep, deer, rabbits, bees, and a variety of fish.

"It's never a good idea to have unhealthy animals," says Oeller. "You don't want the risk of products from unhealthy animals entering the human food supply, you don't want them exposing other agricultural animals to disease, and you don't want wildlife transporting disease-carrying ticks into areas frequented by people. Both from a public health and an animal welfare standpoint, you're better off having healthy animals."

For more information on the Minor Use Animal Drug Program, see the program's Web site at *www.nrsp-7.org* and the FDA's Web site at *www.fda.gov/cvm/index/mums/minortoc.htm.*

Few Drugs for Wild Animals, Pets

Few FDA-approved drugs are available for animals considered to be "minor species." These include wildlife, exotic animals, endangered species, and pets such as birds, rabbits, reptiles, and guinea pigs.

Veterinarians who treat these animals often must rely on unapproved animal drugs or drugs approved for humans or other animals. Sometimes a drug approved for one animal can be used with confidence in another animal with a similar metabolism, says Stephen F. Sundlof, D.V.M., Ph.D., the director of the FDA's Center for Veterinary Medicine. "But when it comes to exotic animals, there is no formula for extrapolating between one species and another—it's a big gamble."

More animal drugs could be available if the Minor Use and Minor Species Animal Health Act is passed by Congress. The "MUMS bill" would establish several new ways to lawfully market new animal drugs while maintaining the rigorous public safety requirements of the FDA.

Linda Bren is a Writer-Editor with the ***FDA Consumer****.*

FIRST INTERNATIONAL CONFERENCE ON MICROBIAL RISK ASSESSMENT

by Gregg Claycamp, Ph.D.

The First International Conference on Microbial Risk Assessment was held in College Park, MD, July 23-25. The meeting drew about 200 risk assessors and food safety professionals from a wide variety of governmental and nongovernmental agencies concerned with food protection, industry and academia. FDA's Acting Commissioner, Dr. Lester Crawford, gave the opening address in which he not only welcomed the participants to the U.S., but also outlined the future of FDA participation in food safety counterterrorism. Counter-terrorism relies on principles of risk analysis to identify hazards, characterize potential exposures from the hazards, and estimate human health risks.

The first day's plenary session included speakers on microbial risk assessment (MRA). Several of the discussions highlighted the rapid growth in the number of "farm-to-fork"

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FIRST INTERNATIONAL CONFERENCE ON MICROBIAL RISK ASSESSMENT (Continued)

risk assessments for food safety assessments and suggested ways in which the process of risk assessment might be improved. A common theme emerging from the talks focused on the tension between the need to perform risk assessments as the basis of public health policy, and the substantial gaps in quantitative information needed to estimate risks.

The remaining two days of the meeting included talks on various phases of risk assessment, including the types of data, data quality, the interfaces between risk assessors and risk managers, risk assessment tools, and case studies of governmental and industry-based risk assessments. Ample time for networking was available during the breaks, reception and the lunches provided on site. Dr. Jean-Louis Jouve, Food and Agricultural Organization of the United Nations, and Dr. Jørgen Schlundt, World Health Organization, presented stimulating lunchtime addresses.

Members of CVM participated in organizing the meeting and in presentations. In particular, Dr. Mary Bartholomew participated on the meeting planning and Dr. Gregg Claycamp presented a plenary talk on antimicrobial resistance risk assessment. Other members of CVM's Risk Analysis Team were in attendance as were CVM staff from a variety of divisions in the Center.

The meeting provided an excellent opportunity for discussions of novel approaches to microbial risk analysis, the gaps in data needed for high-quality risk assessments, and the challenges faced in translating quantitative risk assessments to plain English for risk managers, stakeholders and the public at large. More information about the meeting can be found at the Risk Assessment Clearinghouse web site: *http://www.riskinfoclearinghouse.umd.edu.*

Dr. Claycamp is Director of CVM's Scientific Support & Generic Animal Drug Staff in the Office of New Animal Drug Evaluation.

CVM WORKING WITH OECD ON REQUIREMENTS FOR BIOENGINEERED FOODS AND FEEDS

by William D. Price, Ph.D.

Dr. James Maryanski of FDA's Center for Food Safety and Applied Nutrition (CFSAN) is the leader of the U.S. delegation attending a recent meeting of the Organization for Economic Co-operation and Development's (OECD) Task Force for the Safety of Novel Foods and Feeds. Dr. W. D. Price of CVM's Office of Surveillance and Compliance has been the primary U.S. person developing the compositional consensus documents. The Environmental Protection Agency (EPA), as well as the U.S. Mission to OECD, also has representatives who are involved with the task force meetings.

The Task Force is focusing its work on the development of science based consensus documents that can be used by international bodies such as CODEX, as reference documents in developing guidance and policy for the regulation of bioengineered foods and feeds.

High on the priority of OECD are consensus documents intended to provide technical information related to compositional analyses of important nutrients, toxicants, and other components of plants to aid in safety assessment. Four documents have been completed and declassified, one of which, soybean was authored by the U.S. At a recent meeting, the Task Force reviewed several draft Consensus Documents and set dates for submission of country comments, including documents on maize, sunflower, cotton, and forage legumes. The U.S. is co-authoring the maize document with the Netherlands, and authoring the cotton document. The U.S. will also be collaborating on three new documents.

The Task Force completed plans for a pilot workshop on safety assessment to be held in Moscow, in mid-September, 2002. The workshop is designed to provide information on safety assessment for 30 regulatory officials from the Russian Federation and countries of the former Soviet Union. The Task Force discussed a consensus document on considerations for the safety assessment of animal feeds authored by the U.K., to which the U.S. submitted primary comments, and a revised document will be discussed at the next meeting. The U.S. requested and the OECD Secretariat agreed to prepare a brief paper for consideration at the next meeting that describes procedures for proposals for new projects and review and acceptance (or not) by the Task Force to ensure that countries have adequate opportunity to review new work.

Dr. Price is a Special Assistant in CVM's Office of Surveillance and Compliance.

THE USE OF STEROID HORMONES FOR GROWTH PROMOTION IN FOOD-PRODUCING ANIMALS

The following material is taken from a revised CVM Consumer Information Flier prepared in response to numerous inquiries received about the use of hormones in livestock.

The Food and Drug Administration (FDA) is responsible for ensuring that animal drugs and medicated feeds are safe and effective for animals, and that food from treated animals is safe for humans to eat. Certain steroid hormones have been approved for use at very low concentrations to increase the rate of weight gain and/or improve feed efficiency in beef cattle. No steroid hormones are approved for use in poultry. All of the steroid hormonal growth-promoting drugs are available for over-the-counter purchase in the U.S., and are generally administered by the livestock producer at specific stages of production. Residue levels of these hormones in food have been demonstrated to be safe, as they are well below any level that would have a known effect in humans.

Certain steroid hormones are approved for use at very low concentrations for beef cattle.

Naturally-Occurring Hormones

Estradiol, progesterone, and testosterone are naturally-occurring (endogenous) steroid hormones produced in significant quantities throughout the lifetime of every man, woman, and child, and are required for the proper physiological functioning and maturation of every mammal. All endogenous steroid hormone products marketed in the U.S. for beef growth-promotion are formulated as implantable pellets and are designed to deliver the hormones at a slow, constant rate when injected subcutaneously under the skin of the animal's ear. Numerous scientific studies have demonstrated that, when these drugs are used in accordance with their approved conditions of use, concentrations of the hormones in edible tissues remain within the normal physiological range that has been established for untreated animals of the same age and sex. Because of the slow release of very small amounts of the hormone and a short average half-life (approximately 10 minutes), it has been determined that no preslaughter withdrawal time is necessary to protect the public health. Consumers are not at risk from eating food from animals treated with these compounds because the amount of added hormone is negligible compared to the amount normally found in the edible tissues of untreated animals and that are naturally produced by the consumer's own body.

Synthetic Hormones

Unlike naturally-occurring steroid hormones, there is no natural production of the synthetic compounds, trenbolone acetate, zeranol, and melengestrol acetate (MGA). These compounds are not metabolized as quickly as the naturally-occurring steroid hormones. Therefore, the FDA required, prior to their approval, extensive toxicological testing in animals to determine safe levels in edible tissues for these compounds. Furthermore, FDA required that the manufacturers demonstrate that the amount of hormone left in each edible tissue after treatment is below the appropriate safe level.

Information about approved hormone products can be found in the *Code of Federal Regulations* (CFR), Title 21, Parts 522, 556, and 558. Copies of the CFR may be found at your local public or university library and are for sale from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402. In addition, the *Code of Federal Regulations* may be found on the Internet at *http://www.gpo.gov/nara/cfr/index.html*.

NEW CVM INTERNET SITE PROVIDES EA DOCUMENTS

by Raanan A. Bloom, Ph.D.

The Food and Drug Administration's (FDA's) Center for Veterinary Medicine (CVM) has launched a new internet web site that provides Environmental Assessments (EAs), Findings of No Significant Impact (FONSIs), and Environmental Impact Statements (EISs) for New Animal Drug Applications (NADAs), Food Additive Petitions (FAPs), and Agency-initiated actions. The site may be found at *http://www.fda.gov/cvm/efoi/ea/ea.htm*.

Some of the more requested documents on this site include EAs for bovine somatotropin, ractopamine,

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NEW CVM INTERNET SITE PROVIDES EA DOCUMENTS (Cont.)

ivermectin, enrofloxacin, melengestrol acetate, progesterone and estradiol, and EISs for chloroflurocarbons, antibiotics in animal feed, and selenium.

FDA is required under the National Environmental Policy Act of 1969 (NEPA) to assess potential environmental impacts from their actions. FDA's regulations for implementing NEPA are contained in Title 21 of the *Code of Federal Regulations* (CFR) Part 25. The most recent regulations were published in the *Federal Register* on July 29, 1997 (62 FR 40569) and became effective on August 28, 1997.

NADAs and FAPs submitted to CVM must include a claim for categorical exclusion or an environmental assessment. EAs focus on relevant issues related to the use and disposal of veterinary drugs or feed additives and provide information on soil and water concentrations, environmental fate, and potential effects of compounds released into the environment. EAs are also prepared for certain Agency-initiated actions. If CVM determines that the information in the EA indicates that no significant environmental impacts are expected, then a FONSI is prepared. If significant environmental impacts are identified, then an EIS is prepared.

Most EAs and FONSIs for post-1995 approvals are posted. The Agency will be adding pre-1995 and new EAs and FONSIs as they become available electronically. Many of the EAs on this site were prepared by the NADA or FAP sponsor and were scanned into pdf format. CVM conducted a limited quality assurance review of these documents. Contact the Environmental Safety Staff (HFV-103) with comments or questions about this web site.

Dr. Bloom is a Physical Scientist in CVM's Environmental Assessment Team.

REGULATORY ACTIVITIES

by Karen A. Kandra

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

- Clyde J. Brunner, Co-Owner, Clyde Brunner Farm, New Franken, WI
- Stanley Hall, Owner, Hall & Hall Farm, Limestone, TN
- Tommy D. Carroll, Chuckey, TN
- Bill Lawson, Bill Lawson Livestock, Greeneville, TN
- Chan R. Teel, President, Teel Dairy Farm, Inc., Spokane, WA

The above violations involved illegal residues of gentamicin in cows and neomycin and sulfamethazine in a calf.

A warning letter was issued to Joel G. Newman, President and CEO, United Co-op Farmers, Inc., Fitchburg, MA, for significant deviations from the Current Good Manufacturing Practice regulations for medicated feeds (21 CFR Part 225). This feed manufacturer failed to collect and assay at least three representative samples of medicated feed containing each drug or drug combination used in the establishment at periodic intervals during the calendar year. Although such feeds were produced at this site, no assays were performed in the years 2001 and 2002.

A warning letter was issued to Mark A. Stern, President, Eight In One Pet Products, Inc., Hauppauge, NY, for multiple deviations from the Current Good Manufacturing Practice regulations (21 CFR Part 211), causing drug products, including piperazine citrate syrup for dogs and cats, sulfadimethoxine solution for birds, and aspirin tablets for dogs to be adulterated. Violations included failure to conduct a thorough investigation of unexplained discrepancies or the failure of a batch or any of its components to meet any of its specifications; failure to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process materials and drug products; failure to establish written specifications for active ingredient and excipient components used in drug products; failure to have an individual inventory record of each component and a reconciliation of the use of each lot of such component; failure to maintain a written record of equipment cleaning, maintenance, and use that includes the date and time of usage.

A warning letter was issued to Mrs. Betty L. Mitchell, President, B.L. Mitchell, Inc., Leland, MS, for significant deviations from the Current Good Manufacturing Practice regulations for pharmaceuticals (21 CFR Part 210 and 211). This aquaculture drug repacking operation failed to test incoming bulk iodine disinfectant, nitrofurazone, and container closures to meet product specifications; failed to have a written testing program to assess the stability characteristics of your nitrofurazone products; failure to maintain master packaging and labeling control records; and, failure

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REGULATORY ACTIVITIES (Cont.)

to establish written procedures for packaging and labeling control or cleaning and maintenance of equipment, including utensils. In addition, their nitrofurazone product does not have the required caution statement "HUMAN WARNING: Carcinogenesis: Nitrofurazone, the acting ingredients have been shown to produce mammary tumors in rats and ovarian tumors in mice. Additionally, some people may be hypersensitive to this product. Either wear gloves when applying, or wash hands afterwards."

A warning letter was issued to Steven Boyum, President, Bombay Elevator, Inc., Kenyon, MN, for causing the adulteration of the animal drugs monensin and chlortetracycline within the meaning of Section 501(a)(5) of the Act when they ordered, purchased, and sold those drugs for use in a manner that does not conform to an approved New Animal Drug Application (NADA) in accordance with Section 512. In addition, they caused the adulteration of animal feed since the formulation and labeling of "Custom Mix for Lambs" failed to conform to an approved NADA. They also supplied false, incomplete, and misleading labeling for the medicated feed, stating the improper manufacturer for the product.

FDA PROPOSES NEW INDUSTRY DRAFT GUIDANCE FOR EVALUATING THE SAFETY OF ANTIMICROBIAL NEW ANIMAL DRUGS

The Food and Drug Administration is announcing the availability of a draft guidance document entitled "Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern." This draft guidance discusses a recommended approach for assessing the safety of antimicrobial new animal drugs, an approach that focuses on the microbiological effects on bacteria of human health concern.

FDA's main safety concern is that use of antimicrobial drugs in food-producing animals may lead to the emergence of bacterial pathogens(disease-causing organisms) that may be harmful to humans and that are resistant to drugs used to treat human illness. The emergence of resistant pathogens makes treating human illnesses more difficult.

This draft guidance document discusses a recommended approach for assessing the antimicrobial resistance

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DRAFT VICH GUIDANCES AVAILABLE FOR REVIEW AND COMMENT

FDA's Center for Veterinary Medicine (CVM) is announcing the availability of three draft guidances for industry entitled, "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Repeat-Dose (90-day) Toxicity Testing" (VICH GL #31 FDA/CVM Guidance #147); Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: Developmental Toxicity Testing" (VICH GL #32, FDA/CVM Guidance #148); and "Studies to Evaluate the Safety of Residues of Veterinary Drugs in Human Food: General Approach to Testing" (VICH GL #33, FDA/CVM Guidance #149).

These draft guidance documents were developed by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH).

The objective of these draft guidances is to establish the minimum recommendations for an internationally harmonized testing strategy for determining toxicity of veterinary drug residues in human food. Guidance #147 outlines studies for identifying target organ toxicity after repeating doses (90 days). Guidance #148 provides guidance on the core recommendation for a developmental toxicity study. Guidance #149 outlines a harmonized testing approach to assure human food safety following the consumption of food products derived from animals treated with veterinary drugs.

Draft Guidance documents 147, 148, and 149 are posted on the FDA/Center for Veterinary Medicine Home Page at: *http://www.fda.gov/cvm/guidance/published.htm#documents*. Single copies of the guidances may be obtained by writing to the Communications Staff, FDA/Center for Veterinary Medicine, 7519 Standish Place, HFV-12, Rockville, MD 20855. Please send a self-addressed adhesive label to assist in processing your request.

Written or electronic comments on these draft guidances may be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Electronic comments may be submitted to *http://www.accessdata.fda.gov/scripts/oc/dockets/commentdocket.cfm*. Comments should be identified with the full title of the guidance document and Docket number. The Docket number for Draft Guidance #147 is 02D-0368, 02D-0369 for Draft Guidance #148, and 02D-0326 for Draft Guidance #149. To ensure adequate consideration for comments in preparation of the final document, comments should be submitted by October 4, 2002.

FDA PROPOSES NEW INDUSTRY DRAFT GUIDANCE FOR EVALUATING THE SAFETY OF ANTIMICROBIAL NEW ANIMAL DRUGS (Continued)

concerns as part of the overall preapproval safety evaluation of new animal drugs.

As draft guidance, the document represents the Agency's current thinking on a recommended approach for assessing the safety of antimicrobial new animal drugs with regard to their microbiological effects on bacteria of human health concern. An alternative approach may be used as long as it satisfies the requirements of applicable statutes and regulations.

In particular, the draft guidance describes a methodology sponsors of antimicrobial new animal drug applications for food-producing animals may use to complete a qualitative antimicrobial resistance risk assessment. The draft guidance document outlines a process for integrating relevant information into an overall estimate of risk and discusses possible risk management strategies.

In 1998, FDA announced its intention to consider concerns about antimicrobial resistance, in addition to other factors such as drug residues, when evaluating the safety of antimicrobial new animal drugs. In January 1999, the FDA published a discussion document (framework document) that outlined possible strategies for managing antimicrobial resistance. The draft document describes an approach for implementing concepts from the framework document.

The public may submit comments on the draft guidance to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The full text of the guidance can be found online at: *http://www.fda.gov/cvm/guidance/published.htm*.

This document will stay in draft form for 75 days, giving FDA time to collect and analyze public comments about the guidance.

ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
First Priority, Inc. (ANADA 200-327)	Ivermectin (Privermectin)	Sheep. For treatment and control of various internal parasites.	**ORAL**—The ANADA is a generic copy of Merial Limited's Ivomec Drench for Sheep, approved under NADA131-392. *Federal Register* 08/05/02

NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
DEC International, Inc. (NADA 141-200)	Intravaginal Progesterone Insert (EAZI-Breed™ CIDR® Cattle Insert)	Cattle. For manipulation of estrus.	**INTRAVAGINAL**—The NADA provides for synchronization of estrus in suckled beef cows and replacement beef and dairy heifers, for advancement of first post-partum estrus in suckled beef cows, and for advancement of first pubertal estrus in replacement beef heifers. *Federal Register* 06/20/02
Schering-Plough Animal Health (NADA 141-194)	Diclazuril (Clinacox™), Bacitracin Methylene Disalicylate (BMD®)	Turkeys. For the prevention of coccidiosis, increased rate of weight gain, and improved feed efficiency.	**MEDICATED FEED**—The NADA provides for use of approved single-ingredient diclazuril and bacitracin methylene disalicylate type A medicated articles to make two-way combination drug Type C medicated feeds for growing turkeys. *Federal Register* 07/18/02

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NEW ANIMAL DRUG APPROVALS (Continued)

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Schering-Plough Animal Health (NADA 141-195)	Diclazuril (Clinacox™) Bambermycins (Flavomycin®)	Turkeys. For the prevention of coccidiosis, increased rate of weight gain and improved feed efficiency.	**MEDICATED FEED**—The NADA provides for use of approved single-ingredient diclazuril and bambermycins Type A medicated articles to make two-way combination drug Type C medicated feeds for growing turkeys. The Type C feeds containing 0.91g/ton diclazuril and 1 to 2 g/ton bambermycins are used for the prevention of coccidiosis caused by *E. adenoides, E. gallopavonis*, and *E. meleagrimitis*, and for improved feed efficiency. The Type C feeds containing 0.91g/ton diclazuril and 2 g/ton bambermycins are used for the prevention of coccidiosis caused by *E. adenoeides, E. gallopavonis*, and *E. meleagrimitis*, and for increased rate of weight gain and improved feed efficiency. *Federal Register* 07/25/02

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Pliva d.d. (ANADA 200-232)	Oxytetracycline (Geomycin 200)	Cattle. For treatment of various bacterial diseases.	**SUBCUTANEOUS**—The supplemental ANADA provides for administration of an injectable oxytetracycline solution to cattle, and for its use in lactating dairy cattle. *Federal Register* 07/19/02
Pennfield Oil Co. (ANADA 200-026)	Oxytetracycline Hydrochloride (Pennox 343)	Swine. For the treatment of various bacterial diseases.	**ORAL**—The supplemental ANADA provides for a zero-day preslaughter withdrawal time for use of oxytetracycline hydrochloride soluble powder in the drinking water of swine. *Federal Register* 08/07/02

SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Alpharma, Inc. (NADA 48-761)	Chlortetracycline (Aureomycin 50, 90, 100)	Calves, beef, non-lactating dairy cattle. For the treatment of enteritis and pneumonia.	**MEDICATED FEED**—The supplemental NADA provides for the administration of Type C medicated feeds containing chlortetracycline to cattle as a top dress to deliver 10 milligrams chlortetracycline per pound of body weight daily. These medicated feeds are used for the treatment of bacterial enteritis caused by *Escherichia coli* and bacterial pneumonia caused by *Pasteurella multocida* susceptible to chlortetracycline. *Federal Register* 06/27/02

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SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS (Continued)

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Pharmacia and Upjohn Co. (NADA 140-890)	Ceftiofur Hydrochloride (Excenel® RTU Sterile Suspension) RX	Cattle. For the treatment of acute metritis.	**INTRAMUSCULAR OR SUBCUTANEOUS**—The supplemental NADA provides for injection of ceftiofur hydrochloride in cattle for the treatment of acute metritis (0 to 14 days post-partum) associated with bacterial organisms susceptible to ceftiofur. *Federal Register* 07/11/02
Intervet, Inc. (NADA 121-473)	Fenbendazole (Panacur®)	Dogs. For removal of certain internal parasites.	**ORAL**—The supplemental NADA allows a change from prescription to over-the-counter marketing status of fenbendazole granules for oral use in dogs. *Federal Register* 07/19/02
Elanco Animal Health Division of Eli Lilly & Co. (NADA 140-863)	Ractopamine (Paylean®)	Swine. For increased rate of weight gain, improved feed efficiency, and increased carcass leanness in finishing swine fed a complete ration containing at least 16 percent crude protein.	**MEDICATED FEED**—The first supplemental NADA provides for using ractopamine, a Type A medicated article, used to make Type B and Type C medicated feeds for finishing swine, in a 45-g/lb strength of Paylean and for amending the assay limits for Type B and Type C medicated feeds containing ractopamine. The second supplemental NADA provides for the addition of cautionary statements to labeling. *Federal Register* 07/22/02
Pharmacia and Upjohn Co. **Pair 1** - (NADA 124-309 and NADA 125-476) **Pair 2** - (NADA 138-792 and NADA 138-870) **Pair 3** - (NADA 138-995 and NADA 139-192)	Melengestrol acetate (MGA®) Monensin sodium (Rumensin®) Tylosin phosphate (Tylan®)	Feedlot heifers. **Pair 1** for increased rate of weight gain, improved feed efficiency, and suppression of estrus. (MGA & Rumensin) **Pair 2** all indications for pair 1 and 3 plus the prevention and control of coccidiosis due to *Eimeria bovis* and *E. Zuernii*. (MGA & Rumensin (50 to 360 mg/head/day) & Tylan) **Pair 3** to reduce liver abscesses caused by *Fusobacterium necrophorum* and *Actinomyces pyogenes*. (MGA & Tylan extended to 60 to 90 mg/head/day)	**MEDICATED FEED**—The 6 supplemental NADA's provide for the use of single-ingredient Type A medicated articles containing melengestrol acetate, monensin, and tylosin to make two-way and (with tylosin) three-way, dry and liquid, combination drug Type C medicated feeds for heifers fed in confinement for slaughter. Some of the supplemental NADA's add the single-ingredient monensin claim for prevention and control of coccidiosis in feedlot heifers to the indications for combinations of melengestrol acetate and monensin with and without tylosin. Other supplemental NADA's extend the dose of tylosin to the single-ingredient range of 60 to 90 mg per head per day to reduce the incidence of liver abscesses in feedlot heifers and provide for use of liquid Type C medicated feeds containing melengestrol acetate and tylosin with and without monensin. *Federal Register* 07/22/02

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SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS (Continued)

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Phibro Animal Health, Inc. (NADA 8-804) (NADA 95-143)	Oxytetracycline (TM-50, TM-50D, TM-100, TM-100D, OXTC)	Swine. For treatment of various bacterial diseases.	**MEDICATED FEED:** The two supplemental NADA's provide for use of oxytetracyclineType A medicated articles used for making Type C medicated feeds. The supplemental NADA's provide for a zero-day withdrawal time prior to slaughter when Type C medicated feeds containing oxytetracycline are fed continuously at a dosage of 10 mg/lb of body weight for up to 14 days. *Federal Register* 08/07/02

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