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Feed Safety System Group Initiative Revises Framework Document

by Jon F. Scheid, Editor

The team in the Center for Veterinary Medicine developing the Animal Feed Safety System (AFSS) issued a second draft of its "Framework Document" in December 2006 that says the system will cover all types of feed, including pet foods and all establishments involved in feed manufacturing, packaging, distribution, and use, and that CVM will develop process control regulations to cover all of these aspects of feed manufacturing.

The Food and Drug Administration began the AFSS initiative in 2003 when it announced its intention to make its animal feed safety program more risk-based and comprehensive. The modernized AFSS will incorporate risk-based, preventive control measures for ensuring the safety of animal feed. FDA, with State assistance, has developed and is now refining an AFSS framework document that identifies the current major processes, guidance, regulations, and policy documents that address feed safety and the documents that should be developed to make the Agency's feed safety program comprehensive and risk-based.

The AFSS team released its first Draft Framework Document in 2005. In it, the team introduced the concept of risk assessment to identify and create limits for feed contaminants that were potentially hazardous. The second draft reflects the AFSS Team's refinement of the concepts.

The revised Draft Framework document lists 11 operating principles, up from the 7 listed in the first draft framework (see sidebar, "11 AFSS Principles"), and 5 key components, up from 4 in the original draft (see sidebar, "Components of Animal Feed Safety System"). The four original components were aimed at making sure that ingredients used in feed were safe, rules are in place to limit contaminants, that the methods used to make, distribute, and use feed resulted in safe products, and that all levels had regulatory oversight adequate to address the risk at that level. In the revised Framework, the team highlighted as a component the importance of complete training for inspectors and outreach to the industry to help firms comply with the feed safety rules.

CVM began the AFSS effort because of the gaps in FDA's current system of feed safety oversight. Feed produced in the United States is generally safe. "However," the revised draft Framework says, "because oversight of this industry is limited and focused on a few known safety issues, potential

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CVM Approves Drug to Treat Obesity in Dogs

The Center for Veterinary Medicine in early January 2007 approved the first-ever drug for the management of obesity in dogs in the United States.

The product is Slentrol (dirlotapide), and the sponsor is Pfizer, Inc., New York, NY.

The product will be available only by prescription from a veterinarian.

The drug is given to the dog in varying amounts over the course of the treatment. The dog is given an initial dose for the first 14 days. After that, the veterinarian will assess the dog's progress at monthly intervals, adjusting the dose depending on the dog's weight loss. After the dog has achieved the goal weight, the drug's manufacturer recommends continued use of the drug during a 3-month period, while the veterinarian and dog's owner establish the optimal level of food intake and physical activity needed to maintain the dog's weight.

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human and animal health problems may remain hidden. Recent incidents in which high levels of dioxins were present in mineral supplements used in animal feed reflect these types of hidden risks."

The Framework says that oversight would be risk-based. Not all feed hazards are actually risks, and different hazards present different levels of risk, according to the Framework. It presents a risk equation, which is a hazard multiplied by exposure; the greater the exposure to a hazard (which could be a dangerous

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Eleven AFSS Principles

The Center for Veterinary Medicine's Animal Feed Safety System (AFSS) Team listed 11 "operating principles" in its revised Draft Framework, released in December 2006, including 4 added since the first Draft Framework was released in 2005.

The new principles would extend AFSS to all types of feed and all types of manufacturing, add the concept of flexibility, and emphasize training.

The 11 principles are:

1. The animal feed and animal production industries are responsible for the production, distribution, and use of safe animal feed.
2. The Federal and State regulatory agencies provide the rules, guidance, and oversight to assist industry in producing safe animal feed and feed ingredients.
3. (New) Rules and guidance provide flexibility in the approaches individual producers of animal feed can use to meet acceptable safety criteria.
4. Federal and State regulatory agencies cooperate on all aspects of feed regulation.
5. Feed regulatory agencies conduct inspections of feed-producing facilities, review product labels, sample and analyze feeds for hazards and for compliance with label guarantees, and take appropriate actions to address violations.
6. FDA directs its regulatory resources to those feed-related hazards that pose the greatest risks to animal and public health.
7. Risk-based decision-making is used to help determine which feed-related hazards should receive the highest priority by FDA and the best methods for addressing them.
8. Feed security measures as they relate to counterterrorism should become part of the AFSS.
9. (New) Training is critical for ensuring that industry and regulatory agencies have the most up-to-date knowledge about FDA rules and guidance and for ensuring enforcement by FDA and States is consistent and conducted in an appropriate manner.
10. (New) Feeds intended for food-producing and other types of animals, such as pets, are included in the AFSS.
11. (New) Feed establishments covered in the AFSS include all facilities, equipment, and conveyances involved in the production, storage, packaging, and distribution of individual feed ingredients and mixed feed and the feeding of animals.

CVM Approves Drug to Treat Obesity in Dogs *(Continued)*

Slentrol is a new chemical entity. It is a selective microsomal triglyceride transfer protein inhibitor that blocks the assembly and release of lipoproteins into the bloodstream. Scientists do not completely understand the drug's mechanism for producing weight loss, but it seems to result from reduced fat absorption and by providing a satiety signal from lipid-filled cells lining the dog's intestine.

Adverse reactions include vomiting, loose stools, diarrhea, lethargy, and loss of appetite.

The product is not for use in humans. It carries the standard warning, "Not for use in humans. Keep this and all drugs out of reach of children." The labeling also cites adverse reactions associated with human use, including abdominal distention, abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting.

Many dogs in the United States are overweight and obese. Veterinarians generally agree that dogs weighing 20 percent more than ideal weight are obese.

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Feed Safety System Group... *(Continued)*

contaminant in feed, for example), the greater the risk and the greater the need for oversight under a feed safety system.

The Framework Document enumerates gaps in the current feed safety system under each component and explains how the gap is to be addressed with the revised feed safety system.

For example, the current feed safety system does not fully address all aspects of feed safety from manufacturing to ultimate use, the Framework says. Therefore, the new feed safety system would use process control regulations, supplemented with industry guidance to help explain the regulations.

Public meetings

The AFSS team held its third public meeting in September 2006. More than 100 individuals attended, including several representing foreign countries, which indicated the international interest in food safety.

The previous two meetings were designed to gather input from stakeholders. The AFSS team used the third meeting to present information to stakeholders. The team presented the concept behind the "Health Consequence Scoring" system, which involves two factors—the likelihood of illness, which can be expressed as the potency of the hazard, and the severity of the illness, which in animals can range from reduced feed consumption all the way to death.

The team is planning its next public meeting, to be held in the spring of 2007, to discuss the other aspect of the risk equation—exposure to risks. CVM will announce details of the meeting in the spring.

Components of Animal Feed Safety System

The revised Animal Feed Safety System (AFSS) "Framework Document" the Center for Veterinary Medicine issued in December 2006 presents the proposed AFSS program in five components (listed A through E), identifies gaps under each component, and explains how each will be addressed.

Components	*Gaps*	*How Gaps Are Being Addressed*
Component A Ingredients and the Approval Process	The Food and Drug Administration regulations do not provide a complete listing of ingredients and additives permitted in animal feed.	A Compliance Policy Guide is being developed that will allow FDA to recognize the ingredients defined in the Association of American Feed Control Officials (AAFCO) *Official Publication*. A Memorandum of Understanding is being developed between FDA and AAFCO to identify roles each party plays in adding, modifying, or removing definitions.
Component B Limits for Animal Feed Contaminants	FDA needs a systematic process whereby it can distinguish among feed contaminants based on the risks they pose to animal and human health. FDA needs a process for triggering development of official regulatory methods for detecting contaminants in feed.	A relative risk-ranking system is being developed for internal FDA use. An internal Standard Operating Procedure is being developed.
Component C Process Control for the Production of Feed Ingredients and Mixed Feed	FDA needs a program that covers the feed safety aspects of manufacturing, packaging, storing, distributing, and using medicated and non-medicated feed and feed ingredients. FDA needs to update some aspects of the current Good Manufacturing Practice (cGMP) regulations for medicated feed.	Process control regulations are being developed to require firms to take adequate control steps for the entire feed ingredient and feed manufacturing continuum. Regulations may be updated in response to a petition filed by industry groups and AAFCO that calls for a single set of cGMPs for all medicated feed manufacturers.

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CVM Team Tours Florida Ornamental Fish Facilities

by Jennifer Matysczak, V.M.D., Aquaculture Drugs Team, Office of New Animal Drug Evaluation

In March 2006, six representatives from the Center for Veterinary Medicine (CVM) visited the hub of the U.S. tropical ornamental aquaculture industry in Florida's Hillsborough and Polk counties, as the Center prepares for an expected increase in the number of ornamental fish drugs submitted for review.

The expected increase will be due in part to changes brought about by the Minor Use and Minor Species Animal Health (MUMS) Act of 2004. December 20, 2006, marked the end of the comment period for proposed regulation on indexing, a provision of the MUMS Act. So, now CVM is one step closer to a final regulation that must be in place before sponsors can request the addition of a new animal drug to the index; the final regulation on indexing is due in late 2007.

Indexing and other provisions of the MUMS Act increase the avenues through which safe and effective drugs may become legally available to treat minor species, such as fish. For ornamental fish, the indexing provision may hold the most promise because it provides a way to legally market unapproved new animal drugs for which a complete New Animal Drug Application is not an economically viable option. Indexing will become an option for sponsors after the final rule is published.

CVM is aware of the uniqueness and diversity of aquacultured animals and

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Feed Safety System Group... *(Continued)*

Components of Animal Feed Safety System *(Continued)*

Components	*Gaps*	*How Gaps Are Being Addressed*
Components D Regulatory Oversight	FDA's current regulatory oversight has limited resources and competing priorities and is often based on factors that are not related to actual risk.	A risk-based inspectional approach is being developed for all feed-related inspections.
	FDA's current regulatory approach does not permit adequate inspection of all segments of the industry responsible for manufacturing, packaging, storing, distributing, and using animal feed.	A risk-based inspectional approach is being developed for all feed-related inspections.
	FDA has out-of-date regulations requiring licensed feed mills to report clinical and other experiences associated with those medicated feeds that require the feed mill to be licensed.	Regulations are being updated.
	Counterterrorism efforts are not included in the feed safety aspects of the AFSS, because hazards identified are those that are naturally occurring or result from inadvertent, not deliberate, contamination.	The CVM Counterterrorism Coordinator will keep officials in the U.S. Department of Agriculture, the Department of Homeland Security and other government agencies informed about the AFSS, and obtain their advice.
Component E Outreach and Education	Government feed inspectors and the regulated industries need to fully understand the new regulations before the regulations will be effective.	An outreach plan will be developed; training is being developed for feed inspectors for use when the new regulations go into effect, and as needed thereafter.
	All feed mills do not have access to the most up-to-date "Blue Bird" labeling requirement.	A web-accessible database is being developed to house currently approved "Blue Bird" labeling.

...Florida Ornamental Fish Facilities *(Continued)*

earlier this year sought to learn more about the ornamental aquaculture industry and ornamental fish medicine through on-site and field training.

The team went to Florida, because—with 130-150 ornamental fish farms—the State accounts at a minimum for 80-85 percent of the ornamental fish produced in the United States (some say it is responsible for 95 percent). Ornamental fish is the largest aquaculture commodity in the State; farm gate value in 2005 was $33.2 million, which reflects a $14 million decline due to hurricane losses.

The CVM group consisted of Dr. Donald Prater, Dr. Thomas Letonja, and Dr. Jennifer Matysczak from the Aquaculture Drugs Team, Office of New Animal Drug Evaluation (ONADE); Mr. Charles Eirkson and Dr. Eric Silberhorn from the Environmental Safety Team, ONADE; and Dr. Thomas Moskal from the Post-Approval Review Team, Office of Surveillance and Compliance.

Dr. Roy Yanong, Associate Professor at the University of Florida, and Dr. Kathleen Hartman, an Aquaculture Epidemiologist with the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS), Veterinary Services, organized the training and farm tour schedule.

Tropical Aquaculture Laboratory

During its visit, the CVM team first met with Craig Watson, Director of the University of Florida's Tropical Aquaculture Laboratory (TAL) in Ruskin, FL. Mr. Watson highlighted the history of TAL and discussed special local-need labels for pesticides that it had obtained and research projects it had conducted, and he described major concerns for the industry.

TAL was created in 1996 with a mission to improve the productivity, profitability, and overall success of Florida's ornamental fish industry through applied research and extension and graduate education. Research projects at TAL are applied and diverse. They include:

- Investigations of the effectiveness of sGnRHa and 17α-methyltestosterone;
- Development and effectiveness testing of an autogenous vaccine for *Streptococcus* iniae in red-tail black sharks;
- Determination of the fate of feed in ponds;
- Culture of corals;
- Examination of the growth of *Tridacna* clams under various conditions;
- Study of the diet of introduced Asian swamp eels; and
- Evaluation of various methods in ornamental fish farming of harvesting, grading, and transporting the fish.

Florida ornamental fish farmers typically use seine nets to harvest egg-laying fish from ponds. Florida is the largest producer of ornamental fish in the United States, responsible for at least 80 percent of the country's production.

Mr. Watson led the CVM team on a tour of TAL's facilities. The main office building houses a classroom used for extension workshops and a fish disease diagnostic laboratory.

Dr. Yanong oversees the fish health programs at TAL, including the fish disease diagnostic laboratory, as a major component of his extension program. The diagnostic laboratory performs water quality testing and full health diagnostic workups. Bacterial isolates can be identified in-house and isolates' sensitivities to different antibiotics determined. Tissue samples are sent out for histology and virology when warranted. The diagnostic lab sees cases of fish disease from Florida's commercial fish producers, wholesalers, and retailers, and also from state agencies; the lab saw 258 cases in 2005. In addition, TAL faculty and staff assist producers at their facilities with production and fish health management issues and provide fish health management workshops and extension publications.

In addition to the main office building, TAL has the "hatchery," a quarantine building, living quarters for students, and three greenhouses. Within the hatchery, there is a water quality laboratory as well as research project areas that contain tanks and vats holding species, such as clown loaches, being spawned experimentally by TAL.

The greenhouses have been used for coral propagation, *Tridacna* clam grow-out studies, and various fish research projects.

There are 50 ponds on the 7-acre premises; part of the property was an ornamental fish farm before the university purchased it. The ponds, measuring approximately 30 feet by 70 feet, are within standard production size parameters. Water seeps in from the water table to fill these earthen ponds.

University of Florida

Dr. Ruth Francis-Floyd, Program Director of Aquatic Animal Health at the University of Florida's College of Veterinary Medicine, talked about the aquatic animal health program at the University of Florida. The Fisheries Department has a diagnostic laboratory in Gainesville, FL, that sees approximately 200-250 fish-disease cases each year. The veterinary hospital zoological service sees pet fish cases. Some of the programs that Dr. Francis-Floyd oversees include an aquatic animal medicine residency and continuing education courses, such as Diseases of Warmwater Fish, Advanced Fish Medicine, and Seavet I and II. A University of Florida graduate student,

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...Florida Ornamental Fish Facilities *(Continued)*

Emily Marecaux, had recently completed a study that examined the effect of salinity on the toxicity of potassium permanganate in sailfin mollies.

Dr. Jeff Hill, an Assistant Professor at the University of Florida in the Department of Fisheries and Aquatic Sciences based at TAL, made a presentation to the CVM team in his area of expertise. Dr. Hill's graduate work focused on the ecology of native and non-native predatory fishes in Florida. Prior to his graduate work, Dr. Hill was an African cichlid producer in Miami, FL. He gave the team a primer on invasion biology, discussed risk assessment and mitigation potential, summarized the relevant Florida regulations, and highlighted non-native species found in Florida.

USDA-APHIS

Larry Brashears, a USDA-APHIS Wildlife Services biologist, with an office at TAL, discussed the options available for farmers and other land owners that encounter bird, reptile, or mammal depredation.

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In one of many research projects, the University of Florida's Tropical Aquaculture Laboratory studied the growth of Tridacna clams in these greenhouse systems.

CVM Team Sees Florida Aquaculture Industry Firsthand

A team of animal drug reviewers from the Center for Veterinary Medicine saw firsthand the aquaculture's industry's breadth when the team met with several representatives of that industry during a recent tour of the ornamental aquaculture industry in Florida.

The team met with members of the Florida Tropical Fish Farms Association (FTFFA) for a discussion led by Mr. Art Rawlins, the FTFFA's president. The discussion was a valuable opportunity for CVM team to learn more about the drug needs of the industry and to explain the Investigational New Animal Drug (INAD) process to industry members. Some of the producers participate in INAD studies, and all producers could benefit from the results of the studies.

Carlos Martinez, the State ornamental aquaculture extension and SeaGrant agent at the University of Florida's Tropical Aquaculture Laboratory (TAL) in Ruskin, FL, shared his perspective on the ornamental fish industry with the visiting CVM team. (The SeaGrant program is sponsored by the National Oceanic and Atmospheric Administration [NOAA] of the U.S. Department of Commerce. It is NOAA's primary university-based program in support of coastal resource use and conservation.) Mr. Martinez has seen the industry from the producer's point of view. Immediately before coming to TAL, he owned an ornamental fish farm in Florida. Before that, he operated a shrimp farm in Ecuador for 7 years.

The team visited several fish farms in the area, including 5-D Tropical, Inc., in Plant City, FL, one of Florida's largest ornamental production facilities and importers of ornamental fish. 5-D sells over 800 varieties of fish and produces 92 varieties at their two farms. The CVM team met Jay, Joe, and Damon Diaz. Tony Lott, the farm manager, organized a demonstration of seining of a pond, so the team could see this common method of harvesting fish. Bill Shields and Robin Sanderson showed the team the breeding rooms. Some of the species they breed include barbs, tetras, danios, corydoras, oscars, red-tail black sharks, South American cichlids, and even some amphibians. The CVM group also saw the rooms where fish are packed for shipping.

In Ruskin, the CVM team visited Steve Simmons Aquatics, a farm that produces 15 species of fish—including livebearers and egg-layers—with pond and tank production. There are roughly 300 ponds on the farm. Each pond is roughly one-fifteenth to one-twentieth of an acre in size. Mr. Steve Simmons and his son Ty showed the CVM team around the farm and demonstrated the process of harvesting swordtails from a pond using traps baited with fish food. The farms owners sorted the swordtails for market. Male swordtails have different phenotypic sexual characteristics from females, including the presence of a "sword," or lower extension of the caudal fin. Consumers prefer male swordtails and are willing to pay more for them because of the fish's appearance.

Also in Ruskin are Aquatica Tropicals, owned by Mr. Marty Tanner, and Florida Marine Aquaculture, Inc. Mark

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...Florida Ornamental Fish Facilities *(Continued)*

Concrete burial vaults are commonly used to hold fish in ornamental aquaculture.

Dr. Kathleen Hartman described the role of USDA-APHIS Veterinary Services in aquatic animal health. Dr. Hartman has assisted Florida koi farms with participation in the USDA-APHIS voluntary Spring Viremia of Carp (SVC) surveillance program, has played a role in emergency response within the State, and also has helped develop a volunteer program—the Florida Aquatic Animal Health Plan—with Drs. Yanong and Denise Petty. Dr. Hartman has a courtesy faculty appointment with the University of Florida and is also based out of TAL.

Dr. Hartman gave a presentation about biosecurity as it relates to the ornamental fish industry. Koi farms are perhaps the most stringent in the industry in terms of biosecurity because of the concern over SVC and koi herpes virus.

Florida Department of Agriculture

Kal Knickerbocker from the Florida Department of Agriculture and Consumer Services (DACS), Division of Aquaculture, spoke to the CVM team about Aquaculture Certification and Best Management Practices in Florida. The Best Management Practices cover general pond construction, water effluents, health management, chemical and drug handling, and other requirements.

Not only has DACS made things easier for the farmers by making the Division of Aquaculture a "one-stop-shop" for permitting, but the aquaculture certification that DACS offers provides each farm with a unique identification number that is useful for tracking fish movements.

Florida Aquaculture Industry Firsthand (Continued)

Umlauf showed the CVM team around Aquatica's facilities. In a one-and-a-half acre building, freshwater fish, such as plecostomus and cichlids, are produced in recirculating systems. Martha Campbell gave a tour of her Indo-Pacific marine invertebrate culture and wild marine species holding systems. The team got a close look at the live rock and soft corals that her facility produces and sells.

The team traveled to Plant City, FL, to visit Oak Ridge Fish Hatchery, Inc., which has 400 ponds and produces livebearers, plecostomus, and cichlids. The team met Ruiz Drawdy, the previous owner of the facility, and David and Dustin Drawdy, who currently operate it.

The team also visited Michael Drawdy at Imperial Tropicals, Inc., in Lakeland, FL. The operation has about 400 ponds between two locations. Also, like many other facilities in the ornamental industry, it holds fish in greenhouses in burial vault flow-through systems. Farmers find burial vaults to be the most economical type of holding tank for fish brought in from the ponds. In many cases, it is easier to treat fish that are held indoors than those still in the ponds.

In Gibsonton, FL, the team visited Segrest Farms, one of the world's largest wholesale tropical fish suppliers. Segrest Farms receives, holds, conditions, and ships freshwater and marine fish, reptiles, and aquatic plants. The team met Mr. Elwyn Segrest and toured the facilities with Mr. Jack Bramlett and Dr. Denise Petty.

The Florida Aquarium

The team concluded its visit at The Florida Aquarium in Tampa, FL. This facility opened in March, 1995. Dr. Ilze Berzins, Vice President of Biological Operations and head veterinarian, explained the intricacies of public aquarium medicine. Dr. Berzins discussed the quarantine for animals when they arrive at the aquarium and common medical treatments used on fish in public aquariums. She noted that monogenean parasites are a common problem in aquariums. For its saltwater exhibits, The Florida Aquarium uses natural seawater that is barged in from the Gulf of Mexico and filtered before use.

Additional training

These site visits were only half of a training series on the ornamental fish industry developed for CVM team. Also in March, Drs. Yanong and Hartman lectured for a day at CVM headquarters in Rockville, MD, and coordinated a wetlab with Dr. Renate Reimschuessel at CVM's Office of Research as part of the CVM Staff College's Emerging Technology Series.

CVM's Division of Manufacturing Technologies: Developing an Effective Operation and Motivated Staff

by Jon F. Scheid, Editor

About 10 years ago, as it was implementing its new strategic plan, the Center for Veterinary Medicine (CVM) consolidated into a new division all of its responsibilities for evaluating the drug chemistry, manufacturing, and controls (CMC) portion of a new animal drug application. The CMC evaluation determines a company's ability to continuously produce drugs that meet adequate standards of quality. CVM titled the new group the Division of Manufacturing Technologies (DMT), and named William Marnane as Division Director.

During the 10 years that followed, the consolidated Division was able to coordinate CVM's work with the rest of the Food and Drug Administration (FDA), improve relations with the animal health industry, and build a motivated staff.

Mr. Marnane's managerial skills helped DMT achieve these goals and more. Earlier this year, Center Director Dr. Stephen Sundlof presented Mr. Marnane with the CVM Director's Award, the highest the Center offers, with the citation: "For providing exceptional leadership in the management of personnel and critical manufacturing initiatives important to the mission and goals of the Center."

As part of a look back at the history of CVM during this year of the FDA's Centennial, FDA Veterinarian *interviewed Mr. Marnane, who recently retired, and three DMT staff—Dr. Dennis Bensley Jr., Deputy Director of the Division; Mai Huynh, Supervisory Team Leader in the Division; and Mary Leadbetter, who recently retired as Supervisory Team Leader—to find out how the Division met the challenges.*

CVM put sharp focus on reviewing the manufacturing part of the animal drug application about 10 years ago when it consolidated all parts of that review into the new DMT.

Because of that change, the Center has been able to speak to the animal drug industry with one voice, resulting in less confusion. The new DMT also started new programs, beginning with the Alternate Administrative Process program, but more recently with the Quality by Design (QbD) program, under which drug sponsors can speed the review process if they are willing to do more work before the application is submitted.

At the same time, DMT increased the ability of FDA field inspectors to thoroughly review a manufacturing plant's ability to produce an animal drug. Generalized inspections FDA used before were replaced with specialized inspections, designed to see if the plant could successfully produce the drug as required by the quality criteria specified in the application. This increased scrutiny was not always welcomed by the animal drug industry, but is necessary as animal drug production techniques become more sophisticated.

The DMT is the only pre-market review group within the Center that is involved with manufacturing changes through the entire life of products—"from product birth to death," Mr. Marnane said. The nature of animal drug production and the emphasis on continuous improvement and incorporation of new technology must all be considered during the life cycle of a drug product. Manufacturers frequently change drug substance suppliers and the manufacturing processes during the life of a drug. Analytical methods change, too. CVM must consider all of these post-approval changes within the context of the original approval and the possible effect on safety and efficacy of the drug product, Mr. Marnane said.

Origins of DMT

The decision to place all the manufacturing chemistry portion of drug review into a single division came from an internal review of CVM operations.

Mr. Marnane's deputy, Dr. Bensley, was part of that review team that recommended to Dr. Sundlof that the manufacturing review functions should be consolidated in CVM. "At the time," Dr. Bensley said, "the Division of Chemistry included human food safety and the Chemistry, Manufacturing, and Controls (CMC) review branches. As expected, human food safety issues rather than CMC issues dominated the time of the Division Director" at the expense of the CMC review, he said. He added that part of the CMC review resided in CVM's Division of Surveillance, which "caused a number of problems," including a reduction in CVM's ability to communicate with sponsors on CMC issues with a single voice.

Said Mrs. Huynh, the consolidation of CMC functions into one division gave that birth-to-death consistency in CMC review. It allowed for continuous review by only one Division. The reviewers in the Division

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...Effective Operation and Motivated Staff *(Cont.)*

were able to establish effective new functions "integrating pre-approval inspection and the review of the post-approval annual reports." She said that the creation of the DMT added efficiency of the review and improved communication within the Center as well as with sponsors, "because it allows our reviewers to stay with the same product from pre- through post-approval. It certainly made life easier for our sponsors to always communicate with the same group for CMC related issues."

"The consolidation within CVM gave the Center a much better ability to communicate and work with the rest of FDA," Mr. Marnane added. It also put CVM in a good position to better coordinate with the "field forces" of FDA, who do the pre-approval inspections to make sure facilities are up to the task of producing animal drugs that meet the production standards specified in the sponsor's application.

Pre-approval inspections

The pre-approval inspection of a manufacturing facility's ability to meet current Good Manufacturing Practices (cGMP) is done by FDA's Office of Regulatory Affairs (ORA). However, since its formation, the DMT has gradually increased its role in the pre-approval inspection process and made the inspections more tailored to the standards specified in the drug application.

During his tenure, Mr. Marnane focused attention on coordination with the ORA field forces to achieve a more synergistic outcome. "The heart of a successful pre-approval inspection program is good communication between headquarters reviewers and FDA field investigators. The Division's organizational structure facilitates frequent interactions between pre-market review staff (at CVM) and FDA field investigators. To further enhance communication with the FDA field, reviewers from the Division participate in on-site pre-approval inspections with field investigators to provide technical support when necessary," he said.

CVM officials who review drug applications had little contact with ORA's field inspectors before DMT was formed, Dr. Bensley said. After the DMT was formed in 1996, "we started acquiring more and more" of the responsibility for the technical requirements of the pre-approval inspection program. Today, the program is an integral part of the review and approval process. Because of these increasing responsibilities, "we started having more direct interaction with field personnel, including participation on inspections," he said.

Mr. Marnane said that now when a pre-approval cGMP inspection assignment is sent to the field forces, it frequently "contains requests by the reviewer to focus on specific portions of the manufacturing process."

Bill Marnane, right, led CVM's Division of Manufacturing Technologies from its inception until he retired in January 2007. Dr. Dennis Bensley, Jr., left, is the Division's Deputy.

ORA field inspectors still do the work, but DMT personnel supply technical expertise and information to the field forces, so they can do a more in depth inspection, based on the requirements specific to the drug under review.

According to Mrs. Mary Leadbetter, who recently retired from DMT, "Special areas of interest are communicated to investigators. DMT reviewers have accompanied investigators on inspections as technical experts." ORA inspectors and DMT personnel also train together and jointly attend meetings, she added.

Working with Drug Sponsors

In 1996, the newly formed Division started looking for a more efficient and effective way to work with the animal drug industry, and it developed a program changing the way the industry could report minor manufacturing changes to CVM without filing an application for a supplemental approval. The program, dubbed the Alternate Administrative Process, was developed that same year. It allowed drug sponsors to report minor manufacturing changes on a biennial basis in special reports.

Mr. Marnane and Dr. Bensley developed the concept by working within the existing regulations. Trying to change the regulations would have taken more time and resources than the young Division had to spare. Mr. Marnane and Dr. Bensley presented the concept to CVM management, won approval there, and then "sold" it to industry. "We desperately needed this program, since we were being swamped with supplemental applications," Dr. Bensley said.

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...Effective Operation and Motivated Staff *(Cont.)*

The Alternate Administrative Process lasted only a few years, though. Its goals were taken up a few years later in the FDA Modernization Act (FDAMA), which was effective across the Agency and revamped many of the regulations under which FDA operates. FDA began implementing FDAMA in 1997. "FDAMA actually has had more of a positive impact on our workload than the Alternate Administrative Process by allowing for more reporting mechanisms, depending on the type of change," Dr. Bensley said.

Pharmaceutical cGMP initiative

FDAMA was followed by an FDA initiative, "Pharmaceutical current Good Manufacturing Practices (cGMP) for the 21st Century." The program was designed to improve "FDA's regulation of pharmaceutical quality for veterinary and human drugs...," FDA said in a report. The initiative was started in June 2002 and allows FDA to take into account improvements in pharmaceutical sciences and the lessons learned that FDA acquires from its experience in drug CMC.

The initiative's objectives are:

- Encouraging the pharmaceutical industry to adopt early new technological advances;
- Making sure that FDA's regulatory review, compliance, and inspection policies are based on state-of-the-art pharmaceutical science;
- Facilitating industry's adoption of modern quality management techniques, including implementation of quality systems approaches;
- Enhancing the consistency and coordination of FDA's drug quality regulatory programs, in part, by further integrating enhanced quality systems approaches into the Agency's business processes and regulatory policies concerning review and inspection activities; and
- Encouraging the implementation of risk-based approaches that focus on critical areas.

DMT was heavily involved in this initiative, because it handles the CMC responsibilities.

Mr. Marnane described the initiative as a way to incorporate "the most up-to-date concepts of risk management and scientific advances, encouraging innovation and continuous improvement, to ensure that submission review and cGMP inspections are coordinated and work synergistically."

The initiative looked both at pre-approval product review and at cGMP regulations for ensuring consistent product quality.

Dr. Bensley said that the initiative "is more than just providing opportunities to industry to upgrade its approaches to manufacturing and control. Rather, it emphasizes and allows the use of risk analysis in the decision process." DMT "has always been open to innovative approaches. However, the cGMP Initiative has given us additional leverage to implement or allow the implementation of innovative approaches," he added. In other words, the DMT approach fit well into the Pharmaceutical cGMP Initiative.

One of those innovative approaches, which the initiative embraces, said Mrs. Huynh, is the use of product specialists on inspections. DMT always tried to use specialists, but limited resources and a heavy workload sometimes prevented that. The initiative "has allowed CVM to be recognized for its innovative approach to CMC and cGMP and provided us an opportunity to draft several joint guidances with other Centers," she added.

Industry outreach

Mr. Marnane used the principles of the Pharmaceutical cGMP Initiative to reach out to the animal drug industry.

"Primary among the opportunities provided by the initiative are the concepts of QbD," which, in part, is a means for a sponsor to improve the quality of the submission, Mr. Marnane said. If the concept of QbD is "embraced by drug manufacturers, it could lead to less regulatory burden and shorter review time consistent with DMT's efforts to move toward One-Cycle-Review." The one-cycle review concept suggests that the sponsor will understand what is needed in the drug application completely before submitting it. Therefore, CVM reviewers will not have to send the application back to the sponsor for revisions, which would lead to multi-cycle reviews.

Mr. Marnane said, from a regulatory review perspective, his Division sees QbD "as a demonstration of process knowledge by providing scientific, risk assessment, and quality system information in a pharmaceutical development report" submitted for the application.

According to Dr. Bensley, "QbD is actually an old concept being repackaged as something new." It is based on the idea that quality cannot be "tested into" a product. Instead, it must be built in.

Mrs. Huynh explained that the QbD concept is a "formal way to ask the sponsor to share with us the experiences and lessons learned in product development," to give the CMC reviewers a better idea of the background of the application.

Drug manufacturers are not required to adopt the QbD concept, and the animal drug industry has not yet

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...Effective Operation and Motivated Staff *(Cont.)*

as a whole embraced it. "We do have some sponsors currently using this concept and getting some regulatory relief," Dr. Bensley said. "It is too early to say that it (QbD) will accelerate the approval process; however, those companies that have started using this concept have had higher quality submissions," he added.

In addition, DMT has used the Pharmaceutical cGMP Initiative internally to work toward a one-cycle review for the CMC portion of the review of a drug application.

"As part of the Division's effort to move toward one-cycle review (under the initiative), we also expended a great deal of effort to create a database detailing the type of deficiencies that we encounter in the review of CMC information." The Animal Health Institute and the Animal Drug Alliance—trade associations that represent most of the animal drug manufacturing industry—saw the database as containing "very valuable information that may lead to identifying and correcting areas of CMC submissions where there are recurrent issues leading to applications not being approved," Mr. Marnane said.

Industry, Center relations

Relations between the Center and the animal health industry have from time to time been strained. Under Mr. Marnane, DMT has intensively worked to improve relations with the industry through various meetings and other types of communications.

The improved relationship, he said, "is the result of more and better communication between a well organized Division and its customers." An example of the outreach the Division has undertaken is the series of four workshops the Division helped organize for the pharmaceutical industry on the issue of drug sterilization. These workshops brought FDA review scientists, field investigators, and the pharmaceutical industry together in a common forum to address scientific and inspectional issues.

Dr. Bensley said, "I think we have had a significant improvement in our relationship, especially after the formation of our Division. We readily communicate with the animal drug sponsors and attend a number of meetings every year. Our more recent interactions with the Animal Health Institute and the Animal Drug Alliance include discussions on achieving one-cycle reviews and other CMC issues."

Developing the Division's staff

The Division's staff members, while mostly not new to CVM at the time of DMT's formation, had to adapt to a new organizational paradigm, and Mr. Marnane's job was to get the staff coordinated. He relied on the management strategy Dr. Sundlof introduced to the Center at the same time the Division was formed, called "High Performance Organization (HPO)."

"Building the concepts of the HPO into the Division made sense, because the vision and values (contained in HPO) are consistent with the kind of Division that we wanted to build," Mr. Marnane said. "Quality of life, alignment with Division, Office, and Center goals and objectives, transparency, empowerment, stewardship, metrics, and business-plan-objectives being sought by the Division are all key components of HPO."

Mr. Marnane made it his goal to give the Division staff as much responsibility as possible to achieve the goals. He let his staff make recommendations on bonus awards for individual staff members that were based on performance, interview and recommend candidates for positions within the division, and tackle long-standing issues pertinent to consistent review quality across DMT.

Staff development has resulted in improved work product, Mr. Marnane said. Those improvements developed into an internal "Quality Management System" (QMS) being developed within DMT. Under QMS, the staff helps define the critical elements of the Division's business plan. The business plan must address the Division's mission of determining "whether an animal drug will have and maintain the necessary quality, strength, purity, and identity" for approval.

To make QMS more than a concept, it must be put into place. The implementation plan should include written plan execution procedures, process flow charts and standard operating procedures to document the plan's implementation, adequate staff training, ways to measure the plan's effectiveness, and a mechanism for reviewing and improving the plan, Mr. Marnane said.

Dr. Bensley added, "We are still in the early stages of developing a fully functioning QMS, and this will be an on-going process. There is currently only limited interest from industry, since the Division QMS impacts only our internal processes." However, he said, the Division's ultimate goal is to streamline its business processes, resulting in more efficient review, which he expects should be well received by industry.

Conclusion

As Mr. Marnane prepared to retire from CVM and from government service, he noted several DMT procedural milestones, which help not only point the Division in the right direction, but also give it its identity. DMT has mapped its processes and found out where

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Visitors from Canada's Veterinary Drugs Directorate

In early January, Dr. Siddika Mithani (center), Director-General, and Ms. Kathy Dobbin (right), Director Strategic Planning and Stakeholder Relations, of Health Canada's Veterinary Drugs Directorate (VDD), came to the Center for Veterinary Medicine (CVM) to meet with Center Director Dr. Stephen F. Sundlof (left), and several other members of CVM's management team, to discuss a variety of issues of joint interest, including ways in which the two agencies could enhance their current cooperative activities.

Canada's VDD, like CVM, evaluates and monitors the safety, quality, and effectiveness of animal drugs to protect public and animal health and safety.

Among the topics addressed during the day-long series of meetings were the potential of sharing current Good Manufacturing Practices inspection reports and information on pharmacovigilance activities. The VDD and CVM officials also discussed certain bilateral issues, such as the use in swine of carbadox (which is approved for use in the United States, but not in Canada), aquaculture, and policies on "personal importation" of limited amounts of unapproved drugs from other countries for use in a specific animal.

...Effective Operation and Motivated Staff *(Cont.)*

it needed to place more attention (by performing a "gap analysis"), completed 10 Standard Operating Procedure documents and began another 20, completed the first of what will be annual reviews of the SOPs, and completed its first internal audit.

Mr. Marnane's work has improved the Center's rapport with the industry. "We do believe that CVM's relationship with industry, as it pertains to CMC review, has changed and has improved. The metric used to come to this conclusion is simply the diminishing number of negative comments and the increased amount of positive feedback," he said.

Dr. Bensley said, "The formation of a division to specifically address CMC issues has significantly improved internal and external communications. In addition, it helped by bringing to the forefront that CMC is critical to ensure product quality, safety, and efficacy in animal drug products. The rest is history."

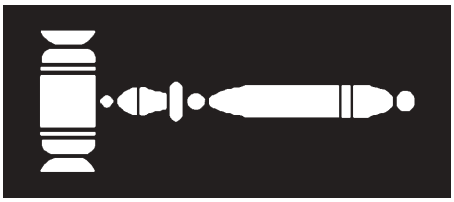
DMT's Director William Marnane

William Marnane was the Director of the Center for Veterinary Medicine's Division of Manufacturing Technology (DMT), a position he held since DMT was formed in 1996 until his recent retirement.

He is a chemist and has a master's degree in biochemistry, which combines organic chemistry and biology. He was a high school science teacher early in his career. He later went to work in the private sector with contracting firms. He entered government service as a research chemist at Walter Reed Army Institute of Research in 1976.

In 1983, he started with FDA in the Center for Drug Evaluation and Research. In 1988, he arrived at CVM, and became branch chief of the Chemotherapeutics Team, Division of Chemistry. In 1996, he became Director of CVM's DMT.

Regulatory Activities for December 2006



A WARNING LETTER was issued to Richard L. Williams, president of Williams Farm, Inc., of North Anson, ME, because an inspection revealed that the firm had offered animals for sale as food that were adulterated under section 402 of the Federal Food, Drug, and Cosmetic Act (FFDCA). Specifically, liver tissues in one of the slaughtered animals in question revealed the presence of the drug flunixin in the amount of 3.372 parts per million (ppm). However, 21 Code of Federal Regulations (CFR) 556.286 sets a tolerance of 0.125 ppm for residues of flunixin in the liver of cattle. Kidney tissues in another slaughtered animal revealed the presence of neomycin residues in the amount of 19.98 ppm; a tolerance of 7.2 ppm has been established in 21 CFR 556.430. The Food and Drug Administration's investigation also found that the firm was holding animals under conditions so inadequate that medicated animals bearing potentially harmful drug residues could enter the food supply. In addition, Williams Farm, Inc., was using flunixin extralabel in violation of section 512 of the FFDCA and of 21 CFR 530.

Similar violations were cited in a WARNING LETTER issued to George C. Palmer and John Palmer, co-owners of Palmer Farms, North Stonington, CT. An investigation revealed that the firm had offered an animal for sale as human food that was adulterated under section 402 of the FFDCA. Specifically, the kidney tissues of the cow in question contained residues of penicillin G procaine at 0.59 ppm. This level was in excess of the tolerance of 0.05 ppm established for residues of this drug in the uncooked edible tissues of cattle as codified in 21 CFR 556.510. The investigation also found that animals were being held under conditions so inadequate that medicated animals bearing potentially harmful drug residues were likely to enter the food supply. Treatment records and an adequate inventory system were also lacking. Among other violations cited, the firm administered penicillin G procaine without following the dosage level, route of administration, and withdrawal period for cattle set forth in the approved labeling, and the administration was done without the supervision of a licensed veterinarian in violation of 21 CFR 530. FDA investigators also observed a number of expired new animal drugs in the firm's storage area; the use of these would be a violation of section 512 of the FFDCA.

Sulfadimethoxine residues in the liver and muscle tissues of a cow offered for sale as human food exceeding the established tolerance set forth in 21 CFR 556.640 resulted in the issuance of a WARNING LETTER to James and Gregory Rickert, owners of Rickland Farms, LLC, Eldorado, WI. Specifically, the presence of sulfadimethoxine in the animal's muscle tissue at 0.64 ppm and in its liver tissue at 0.74 ppm caused the animal to be adulterated within the meaning of section 402 of the FFDCA, because a tolerance in such tissues has been set at 0.1 ppm. The firm was also cited for using sulfadimethoxine, spectinomycin, and neomycin extralabel in violation of sections 501 and 512 of the FFDCA and of 21 CFR 530. In addition, the firm was found to be holding animals under conditions that were so inadequate that medicated animals bearing potentially harmful residues were likely to enter the food supply. Adequate treatment records were also found to be lacking at the firm.

Comings and Goings

New Hires

Office of the Director

- Laura Alvey, Director, Communications Staff

Office of New Animal Drug Evaluation

- Emily Smith, Staff Fellow
- Holly Erdely, Staff Fellow
- Annette McCarthy, Biologist
- Achintya Pal, Staff Fellow

Office of Management

- Holly Balance, Staff Specialist

Departures

Office of the Director

- Andrew Beaulieu, Special Assistant to the Director
- Linda Grassie, Director, Communications Staff

Office of New Animal Drug Evaluation

- William Marnane, Director, Division of Manufacturing Technologies
- Jacquelyn Pace, Regulatory Policy Analyst
- Benjamin Puyot, Consumer Safety Officer
- Denzil Walker, Writer/Editor

Office of Surveillance and Compliance

- Gloria Dunnavan, Director, Division of Compliance
- John Matheson, Senior Regulatory Review Officer

Office of Research

- David Batson, Deputy Director

Office of Management

- Patricia Carr, Management Officer
- David Grau, Senior Management Officer Consultant

Approvals for December 2006 and January 2007

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

SLENTROL (dirlotapide) Oral Solution (NADA 141-260), filed by Pfizer, Inc. The NADA provides for the veterinary prescription use of dirlotapide solution in dogs for the management of obesity. Notice of approval was published January 4, 2007.

DEXDOMITOR (dexmedetomidine hydrochloride) (NADA 141-267), filed by Orion Corp. The NADA provides for the veterinary prescription use of dexmedetomidine hydrochloride injectable solution as a sedative, analgesic, and pre-anesthetic in dogs. Notice of approval was published January 4, 2007.

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

RESPIRAM (doxapram hydrochloride), an injectable solution (ANADA 200-435), filed by Modern Veterinary Therapeutics, LLC. The ANADA provides for use of RESPIRAM (doxapram hydrochloride) in dogs, cats, and horses to stimulate respiration during and after general anesthesia. Modern Veterinary Therapeutics' RESPIRAM is approved as a generic copy of DOPRAM-V Injectable, sponsored by Fort Dodge Animal Health, Division of Wyeth, under NADA 034-879. Notice of approval was published January 4, 2007.

GENTAMICIN SULFATE INJECTION (ANADA 200-394), filed by Sparhawk Laboratories. The ANADA provides for the use of Gentamicin Sulfate Injection in piglets up to 3 days old for treatment of porcine colibacillosis caused by strains of *Escherichia coli* sensitive to gentamicin. Sparhawk Laboratories' Gentamicin Sulfate Injection is approved as a generic copy of Schering-Plough Animal Health Corp.'s GARACIN Piglet Injection, approved under NADA 103-037. Notice of approval was published December 22, 2006.

PRIMEX (pyrantel pamoate) (ANADA 200-445), filed by First Priority, Inc. The ANADA provides for the use of pyrantel pamoate in horses and ponies as an OTC animal drug product for the removal and control of various internal parasites. First Priority, Inc.'s, PRIMEX Horse Wormer is approved as a generic copy of Pfizer, Inc.'s, PAMOBAN Horse Wormer, approved under NADA 91-739. Notice of approval was published December 4, 2006.

(Continued, next page)

Approvals for December 2006 and January 2007 *(Continued)*

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

RUMENSIN 80 (Monensin) Type A medicated articles (NADA 95-735), filed by Elanco Animal Health, a Division of Eli Lilly & Co. The supplemental NADA provides for the use of an increase in the upper dose limit of monensin to 40 g/ton (480 mg/hd/day) in Type C medicated feeds used for improved feed efficiency, and for the prevention and control of coccidiosis due to *Eimeria bovis* and *Eimeria zuernii* in cattle fed in confinement for slaughter. Notice of approval was published January 8, 2007.

NOLVASAN (chlorhexidine acetate) (NADA 9-782), filed by Fort Dodge Animal Health, a Division of Wyeth. The supplemental NADA provides for the revision of labeling of the product, which is approved for the use of (chlorhexidine acetate) Antiseptic Ointment as a topical antiseptic for superficial wounds of dogs, cats, and horses. The supplement provides for a revised food safety warning on labeling, specifically to warn against the use of the product in horses intended for human consumption. Notice of approval was published January 4, 2007.

ANTISEDAN (atipamezole hydrochloride) (NADA 141-033), filed by Orion Corp. The supplemental NADA adds a claim for reversal of sedative and analgesic effects of dexmedtomidine hydrochloride to labeling for atipamezole hydrochloride injectable solution, which is already approved for reversal of the sedative and analgesic effects of medetomidine hydrochloride in dogs. Notice of approval was published January 4, 2007.

NUFLOR (florfenicol) 2.3% Concentrate Solution used to make medicated drinking water for administration to swine for the treatment of respiratory disease associated with several bacterial pathogens (NADA 141-206), filed by Schering-Plough Animal Health Corp. The supplemental NADA revises the nomenclature for a respiratory pathogen in the label claim. Notice of approval was published January 4, 2007.

CLOMICALM (clomipramine hydrochloride), filed by Animal Health US, Inc. (NADA 141-120). The supplemental NADA provides for the veterinary prescription use of CLOMICALM (clomipramine hydrochloride) Tablets for treatment of separation anxiety in dogs. The effect of the supplement is the addition of a 5 mg tablet size. Notice of approval was published January 4, 2007.

TYLAN (tylosin phosphate) Type A medicated articles (NADA 12-491), filed by Elanco Animal Health, A Division of Eli Lilly & Co. The supplemental NADA provides for use of TYLAN (tylosin phosphate) Type A medicated articles for an alternate feeding regimen for the control of swine proliferative enteropathies (ileitis) associated with *Lawsonia intracellularis*. In addition, Elanco Animal Health revised the names of other enteric pathogens of swine to reflect changes in the scientific nomenclature for these bacteria. Notice of approval was published December 12, 2006.

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