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CVM NAMES TWO TO SENIOR POSTS

by Joanne M. Kla

The Center for Veterinary Medicine has recently filled the positions of Director, Office of Research and Deputy Director of the Office of New Animal Drug Evaluation.

Effective January 15, 2003, Dr. Linda Youngman accepted the position of Director, Office of Research (OR), on a permanent basis succeeding Dr. Norris Alderson. Dr. Youngman has been acting director for the past 1½ years. "During this time, she has demonstrated the leadership, team work and commitment that has been so important to the continuing success of OR and CVM. During her tenure, the quality of OR's science has received high recognition and the productivity of OR's scientists has remained high," said Dr. Stephen Sundlof, CVM Director. Dr. Youngman served as Deputy Director of OR from August 2000 to July 2002.

Photo by Karen Kandra

Dr. Linda Youngman

Prior to coming to CVM, Dr. Youngman worked at the University of Oxford (UK), Clinical Trial Service Unit & Epidemiological Studies Unit, as the Director of Laboratories responsible for conducting large, human clinical trials and epidemiological studies worldwide.

Dr. Youngman earned her B.S., M.S., and Ph.D. degrees from Cornell University in toxicology and biochemistry. She also received post-graduate training in Epidemiology and Medical Statistics at the London School of Hygiene and Tropical Medicine.

Dr. Bernadette Dunham joined CVM on December 16, 2002, as the new Deputy Director for the Office of New Animal Drug Evaluation (ONADE). ONADE's major responsibility is to review information submitted by drug sponsors to determine if data are adequate to support a drug's approval for marketing. Dr. Dunham comes to CVM from the American Veterinary Medical Association's Governmental Relations Division in Washington, D.C., where she was serving as Acting Director. Dr. Dunham had been with AVMA since 1995.

Photo by April Demert

Dr. Bernadette Dunham

"I have worked with Bernadette for several years. I have a great respect for her accomplishments and professionalism in advancing AVMA's mission, and I am very gratified that she has elected to work for CVM," said Dr. Stephen Sundlof, CVM Director.

Dr. Dunham received her D.V.M. from the Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada. She was in private practice

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CVM NAMES TWO TO SENIOR POSTS (Continued)

(companion animal) in Ontario for three years before moving to Boston, MA, where she received her Ph.D. from Boston University. Following her post-doctoral studies in Boston, she participated in a residency program in the Department of Pathology at the New York State College of Veterinary Medicine, Cornell University. In 1988, Dr. Dunham joined the faculty of the Department of Pharmacology at the State University of New York (SUNY) Health Science Center, Syracuse, NY where her research focused on the molecular regulation of cardiac gap junction proteins. Concurrently, she was the Director of Laboratory Animal Medicine, Department of Laboratory Animal Resources, from 1989-1995 at the SUNY Health Science Center, Syracuse, NY.

Dr. Dunham is also an Adjunct Professor with the Department of Biomedical Sciences and Pathobiology at the Virginia-Maryland Regional College of Veterinary Medicine in Blacksburg, VA, a position she has held since 1996. She lectures on a variety of topics from emerging issues and opportunities in veterinary medicine to the role of consensus building in policy development.

As Acting Director of the Governmental Relations Division (GRD) at AVMA, Dr. Dunham was responsible for directing and supervising the activities of the staff to ensure that all GRD operations complied with the objectives and mission of the AVMA as set by the AVMA Executive Board. She participated in the formation and execution of association policies, objectives, and programs as they relate to the association's strategic plan; with particular emphasis on Federal legislative and regulatory issues. Dr. Dunham's work also involved identifying Congressional and regulatory issues that may impact on the profession as well as developing strategies for response to these issues.

Joanne Kla is a Consumer Safety Officer on CVM's Communications Staff and Assistant Editor of the FDA Veterinarian.

A CONTEMPORARY APPROACH TO RISK ANALYSIS IN GFI #152

by H. Gregg Claycamp, Ph.D.

In the FDA's mission "to promote and protect the public health . . . and [monitor] products for continued safety after they are in use," the Agency relies regularly on the principles and practice of risk analysis. CVM is likewise using risk analysis for approving new animal drug applications, in surveillance and compliance activities, and for its business planning. This essay describes the risk assessment model recently adapted by CVM for antimicrobial resistance risk assessment.

Risk analysis encompasses four major elements: hazard identification, risk assessment, risk management, and risk communication. These elements include the processes by which public health agencies recognize public health hazards, prioritize resources to prevent or mitigate health risks, monitor the successes and failures of public health initiatives, and communicate hazards and risks to the public and industry stakeholders. Two of the four activities, hazard identification and risk assessment, rely primarily on objective scientific and statistical methods—the *facts* of hazards and risks. The remaining two activities, risk management and risk communication, involve consideration of legal and economic constraints, cost-benefit analysis, and public tolerance for risk—the societal *values* pertaining to hazards and risks. For many public health risks, the natural tendency for tension between objective and subjective processes or between societal values and economic limits to resources for risk management often embroil risk analyses in lively and prolonged debates.

Risk assessment is a process in risk analysis in which information about the potential exposures to identified hazards is analyzed in order *to inform a risk decision* to be made by risk managers. Risk, broadly

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FDA VETERINARIAN

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A CONTEMPORARY APPROACH TO RISK ANALYSIS . . . (Cont.)

defined as *exposure to a chance of loss*, can arise in almost any activity in life. Most individual decisions to engage in risky activity or exposure are made intuitively— i.e., accomplished immediately and without conscious use of reasoning— and without the need to analyze the probability of harm, the quantity of exposure, and the subsequent probability of loss. For example, it is known by anyone past a very young age that crossing a busy street involves *exposure* to the *hazards* of moving vehicles and the *risk* of injury or death. It is unlikely that anyone would commission a quantitative study to inform the personal decision to cross the street: this decision is made intuitively. Yet, the incredible breadth of risk analysis in human endeavors is evident in the fact that a team of municipal risk managers might approach essentially the same risk decision (to define a crossing point on the same busy street) by commissioning a formal risk assessment to inform their decisions about how to manage the risk. Both the mind's intuitive process and the formal process capture qualitatively the same kinds of information for the decision about crossing: the nature of the hazard (i.e., trucks, cars, or bicycles), the magnitude of potential exposure (traffic density), and the likelihood of successful crossing. The difference between the two decisions is largely in the degree of sophistication of the analyses and the formality of the decisionmaking steps.

Risk assessment is a process in risk analysis in which information about the potential exposures to identified hazards is analyzed in order* to inform a risk decision *to be made by risk managers.

The past few decades have witnessed an exponential increase in our understanding of health risks and of how to use risk assessment to inform risk management decisions to allocate scarce resources for the management or prevention of public health risks. Numerous risk analysts and theorists have participated in this growth by contributing to the development of risk analysis paradigms that can capture the logical reasoning and technical know-how in their respective scientific fields. Very recently, CVM contributed to these developments by proposing a qualitative risk assessment process for pre-market approvals of antimicrobial new animal drugs.[1] Although CVM's qualitative model adapts a contemporary approach to risk assessment, it is based on the fundamental scientific principles shared by all risk assessment paradigms.

Similar to most contemporary health risk assessment models, the CVM model in Guidance for Industry (GFI) #152 evolved from The National Research Council report to the National Academy of Sciences (NAS), *Risk Assessment in the Federal Government: Managing the Process*.[2] This report, also known as the "Red Book" for its red cover, is often cited as providing the definitive paradigm for risk assessment. Although developing a paradigm was not one of the committee's charges, the risk assessment model evolved naturally from the committee's consideration of "the current practice of risk assessment and its relation to the process of regulations of hazards to human health." Viewed with the clarity of hindsight, the committee's outline of the common processes used in health risk assessment helped to focus a discussion among risk assessors toward defining risk assessment paradigms that have broad applicability in public health.

According to the Red Book, risk assessment is "the characterization of the potential adverse health consequences of human exposures to environmental hazards" (p.18). Although the definition is often modified to fit specific types of hazards, it is generic enough to suffice as a basic definition for this discussion. The risk assessment process was divided into four processes ("steps") of hazard identification, dose-response assessment, exposure assessment, and risk characterization. The first three processes are combined in the risk characterization process to produce the risk assessment that informs risk management decisions.

The past few decades have witnessed an exponential increase in our understanding of health risks and of how to use risk assessment to inform risk management decisions to allocate scarce resources for the management or prevention of public health risks.

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A CONTEMPORARY APPROACH TO RISK ANALYSIS . . . (Cont.)

Hazard identification, the first step in the Red Book model, answers the question, "Can the biological, physical, or chemical agent cause an adverse health effect in humans, given an exposure?" In some if not most health risk assessments, hazard identification is retrospective, derived from observations in epidemiological studies of associations between exposures to specific hazards and the occurrence of adverse health effects.

In the second step of the four-step paradigm, the focus is on *how much* of the hazardous agent is necessary to be ingested, inhaled, or absorbed to elicit an adverse health effect in the exposed individuals. This information is needed not only to understand the severity of the risk, but also to project future risk given a projected exposure.

The third step of the four-step paradigm, exposure assessment, deals with the question of how much of the hazardous agent is presented to the individual or "receptor" in various environmental (including dietary) pathways. A complete exposure assessment estimates the duration, intensity, and likelihood of exposures of a given intensity and duration occurring in a given population or individual.

Finally, risk characterization is the step in which the results of the other three steps of risk assessment are analyzed and risk is estimated. Risk characterization considers the quality of the data, the likelihood that plausible cause and effect (biological) models have been proposed, and the statistical uncertainty in the overall estimate of risk. While still part of the overall "objective" process of risk assessment, risk characterization usually reviews multiple risk scenarios (derived from multiple exposure scenarios) and relies on professional judgment for identification of the most appropriate scenario(s) for risk estimation.

Public Understanding

During the past two decades, there has been much growth in the public's understanding of risk and risk analysis. Additionally, numerous risk scholars and practitioners discussed the merits of various risk analysis paradigms for diverse kinds of hazards and adverse health outcomes. Out of this discussion has developed an understanding of the recursive nature of risk analysis: health hazards are identified and prioritized for attention, risks from exposures to the hazards are assessed, risk management decisions are made, and—given new information about the risks—the process repeats itself in a new prioritization of the health hazards. A second realization about risk analysis is that some health hazards are identified but a formal risk assessment is not initiated due to scarce risk assessment resources. Finally, public interest in health risks, coupled with increasing demands for transparency in governmental decision making, have led to growth in risk communication as a distinct and important process within risk analysis. These features have combined to justify the contemporary approaches to risk analysis.

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GENERALIZED COMPONENTS OF RISK ASSESSMENT FROM GFI #152.

RELEASE ASSESSMENT

The release assessment describes the probability that factors related to the antimicrobial new animal drug and its use in animals will result in the emergence of resistant bacteria or resistance determinants in the animal.

EXPOSURE ASSESSMENT

The exposure assessment describes the likelihood of human exposure to the hazardous agent through particular exposure pathways. The exposure assessment should provide a qualitative estimate of the probability of this exposure occurring.

CONSEQUENCE ASSESSMENT

The consequence assessment describes the relationship between specified exposures to a biological agent (the hazardous agent) and the consequences of those exposures.

RISK ESTIMATION

The risk estimation integrates the results from the release assessment, exposure assessment, and consequence assessment to produce an overall estimate of the risk. All three elements of the risk assessment process are important contributing factors and should be integrated and considered as a whole when assessing the risk.

A CONTEMPORARY APPROACH TO RISK ANALYSIS . . . (Cont.)

CVM's Risk Assessment Model in GFI #152

The evolution of risk analysis continues as CVM adapts contemporary risk analysis for approvals of antimicrobial new animal drugs for food animal uses. The proposed model in GFI #152 is an adaptation of the paradigm proposed by the Office International des Epizooties (OIE) (Figure 1).[3] CVM believes that this contemporary model offers a convenient compartmentalization of the information needed for specialized risk assessments in NADAs as they apply to issues in human food safety. For example, the human food exposure pathway for either residues of animal drugs or resistance determinants from the use of animal antimicrobial drugs is a complex exposure beginning on the farm and ending in the human intestine. CVM believes that it is convenient to compartmentalize the animal-based components of the risk assessment paradigm in the release assessment and the human-dominant factors in the remaining portion of exposure assessment.

The departures of the CVM paradigm from the classical, four-step paradigm are first, the exposure assessment phase is divided into two parts, release assessment and exposure assessment and, second, consequence assessment is used in place of the more narrowly defined concept of dose-response assessment from the Red Book's four-step paradigm. Otherwise, the organization of the steps or elements of risk analysis are similar to those widely used in the practice of health risk assessment.

A final note on contemporary risk assessment paradigms: risk analysis paradigms are logical processes and frameworks for the organization of information to inform a risk management decision. It should be apparent that the goal is to bring organized and high-quality risk information to a risk management decision. Thus, flexibility in how this is accomplished is mentioned in the preamble to GFI #152: "An alternate approach may be used as long as it satisfies the requirements of applicable statutes and regulations**.**" In fact, contemporary risk analysis is a process that encourages deliberation and analysis under a goal of reducing uncertainties in risk management decisions. CVM recently invited comments on the proposed Guidance and will continue to encourage new ideas and methods for using risk assessment to inform risk management decisions.

Dr. Claycamp is Director of CVM's Scientific Support & Generic Animal Drug Staff.

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[1] Guidance for Industry #152, "Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to Their Microbiological Effects on Bacteria of Human Health Concern." See *http://www.fda.gov/cvm/guidance/dguide152.pdf*.

[2] National Research Council, Risk Assessment in the Federal Government: Managing the Process Washington, DC: National Academy Press, (1983). See *http://www.nap.edu*.

[3] OIE Ad hoc Group on Antimicrobial resistance, Office International des Epizooties, Organisation Mondiale de la Santé Animale (World Organization for Animal Health), Guideline No. 1, *Risk Methodology for the Potential Impact on Public Health of Antimicrobial Resistant Bacteria of Animal Origin*.

LEVERAGING EXAMPLES – PART III: CRADAS

by Marilyn Martinez, Ph.D.

This third article on leveraging initiatives at the FDA Center for Veterinary Medicine (CVM) describes two Cooperative Research and Development Agreements (CRADA's) and illustrates the breadth of issues that can be the subject of a CRADA and the activities that go into the development of a CRADA.

WHAT IS A CRADA?

A CRADA is an agreement between one or more FDA Centers/Laboratories and one or more non-Federal parties. The FDA Center/Laboratory provides personnel, services, facilities, equipment, or other resources toward the conduct of specified research or development efforts. Such research must be consistent with the mission of the Center/Laboratory. The CRADA partner contributes one or more of the above and may contribute funding to the project. More detailed information on CRADAs can be obtained at the following websites: *http://www.fda.gov/oc/ofacs/partnership/techtran/policyst.htm* and *http://www.fda.gov/oc/ofacs/partnership/techtran/crada.doc*.

Once a CRADA concept is developed, it must go through extensive internal review and approval both

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LEVERAGING EXAMPLES – PART III: CRADAS . . . (Continued)

within the Center originating the proposal and through the Agency. To be executed, the proposal must be approved by the participating FDA Center Director, FDA's CRADA Review Board, the Commissioner of the FDA, and the non-Federal party. Principal Investigator(s) (PIs)

A CRADA is an agreement between one or more FDA Centers/Laboratories and one or more non-Federal parties.

must be designated, serving as the Federal government representative(s) responsible for the scientific and technical conduct of the project.

EXAMPLES OF EXECUTED CRADAS

The remainder of this article will describe two very different examples of executed CRADAs involving CVM:

- Quality of Animal Drug Submissions
- Enhancing Clinical Drug Trial Simulation and Population PK Analysis Software to Improve the Drug Development Process

QUALITY OF ANIMAL DRUG SUBMISSIONS

Research Objective – To provide CVM with information on those areas where sponsors need additional guidance for developing quality submissions and to help CVM identify areas for improvement with regard to its own communication and interactions with the regulated industry.

CRADA Description – CVM and Riviere Consulting entered into a CRADA to identify and address issues regarding the quality of new animal drug applications submitted to the FDA. For a fee, animal drug sponsors can retain Riviere Consulting to provide a pre-submission review of applications in an effort to evaluate the application's compliance with applicable FDA regulations and guidance documents. Riviere Consulting may attend meetings between CVM and the drug sponsor to assist the drug sponsor in understanding CVM's requests and to provide a critique of CVM/Industry interactions as feedback for CVM. Such a critique focuses on the quality of questions CVM asks of the sponsor and the clarity of the observed communications. Thus, the interactions between Riviere Consulting and drug sponsors are intended to serve two important functions:

1. Help firms develop a quality submission, thereby enabling CVM to spend more time focusing on the scientific contents of the submission.
2. By observing the interactions between FDA and both new and established drug companies, Riviere Consulting can provide important neutral party feedback to CVM on the strengths and weakness of these interactions:
   - ✧ Insight into where additional guidance is needed.
   - ✧ Ideas regarding how CVM can best communicate this additional guidance to both large and small companies.
   - ✧ Examples of when CVM failed to adequately communicate with drug sponsors in written and oral communications.

As part of this agreement, Riviere Consulting provides semiannual reports to CVM that help identify causes for poor quality submissions and suggests mechanisms that may help CVM to better meet the needs of its customers. Points addressed in these semiannual reports include:

1. A summary of all CRADA activity occurring during the six month reporting period including a list of sponsors who retained the services of Riviere Consulting, any termination of agreements, and a summary of whether advice was followed. It should be noted that due to the time required to develop the necessary client associations, for sponsors to generate submissions, and for Dr. Riviere to provide submission review, there may be minimal information to convey over one or several reporting periods.
2. Comments received by Riviere Consulting from the regulated industry pertaining to this CRADA concept.
3. Observations regarding CVM's availability and willingness to respond to questions or issues relating to New Animal Drug Applications.
   - ✧ CVM-CRADA partner interactions
   - ✧ CVM-drug sponsor interactions
4. Input received from the drug sponsors regarding where additional information or guidance is needed with regard to CVM's expectations.
5. The clarity of CVM's correspondence (teleconferences, meetings, letters).

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LEVERAGING EXAMPLES – PART III: CRADAS . . . (Continued)

6. The willingness of drug sponsors to communicate with CVM (and any observed or perceived reasons for communication barriers).
7. Insights into fundamental reasons CVM receives poor quality submissions. These comments relate to the nature of the problem with submissions and how they can be corrected.
8. Technical sections (or components thereof) that have the greatest number of problems.
9. Suggestions for CVM actions that could facilitate the development of higher quality submissions.

Through this effort, CVM hopes to optimize the efficiency of the application review process and improve our interactions with the regulated industry.

For additional information with regard to this CRADA, please refer to *http://www.fda.gov/cvm/index/cradacvm/CVMCRADA01.doc* and *http://www.riviereconsulting.com/.*

Enhancing Clinical Drug Trial Simulation and Population PK Analysis Software to Improve the Drug Development Process

Research Objective – To examine the use of *in silico* methods for addressing complex scientific issues impacting the regulation of animal drug products and to assist in the optimization of clinical study designs.

CRADA Description – Computer-assisted trial design (CATD) is a form of modeling and simulation technology that can be used by a scientific team to develop "virtual clinical trials." It consists of a series of Monte Carlo simulations to approximate a distribution of possible outcomes for a specified set of model conditions, parameter attributes, and assumptions. By repeating the simulations over a range of conditions, the scientific team can test the impact of study design elements and sources of variability or uncertainty on trial outcome. This allows for the optimization both of dosages used in the clinical trial and the conditions under which the trial is executed. It also facilitates the integration of multiple sources of data, thereby expanding the ability to predict the impact of drug or drug use variables.[1] Thus, CATD is a tool for maximizing the information derived from existing sources of data and for examining the potential outcomes associated with a range of doses and dosing regimens.

The original CRADA was only between the Center for Drug Evaluation and Research (CDER) and Pharsight. However, great interest in the potential use of this tool was expressed by the Center for Biologics Evaluation and Research (CBER) and CVM. Since the CRADA had already been reviewed and approved by the FDA CRADA Review Board, the addition of CBER and CVM to the existing CRADA did not require additional review. Thus, with the agreement of all parties, CBER and CVM were added to the CRADA partnership.

Within the scope of this CRADA, Pharsight brings scientific software development experience, a base of state-of-the-art scientific software products, and extensive experience drawn from both industry and academia. CDER, CBER, and CVM bring FDA's scientific regulatory expertise and years of experience in the review of drug applications to provide suggestions with regard to potential software modifications for future versions of this software.[2]

For additional information on CATD, refer to *www.Pharsight.com*.

CONCLUDING COMMENTS

Due to the rapid pace at which science and technology are progressing, leveraging has become essential in optimizing the efficiency of FDA-related activities and for expanding the Agency's resource base. The CRADA is one mechanism through which such leveraging activity may occur. For points to consider and policies regarding the development of a CRADA with the FDA, please refer to *http://www.fda.gov/oc/ofacs/partnership/techtran/policyst.htm*.

If you have any questions on leveraging or if you have any interest in initiating a collaboration with CVM please contact David Batson at (301) 827-8021.

Dr. Martinez is a Senior Research Scientist in CVM's Office of New Animal Drug Evaluation.

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[1] Presented by Dr. Peter Lee, Associated Director, Pharmacometrics, Office of Clinical Pharmacology and Biopharmaceutics, FDA at the AAPS short course on Computer Simulation and its Role in Drug Development Research, January 28-29, 2002.

[2] Pharsight News Release, Feb 13, 2001 *http://www.pharsight.com/news/release.php?news_id=35*

CVM PARTICIPATES IN PEW INITIATIVE MEETING ON TRANSGENIC ANIMALS

by Wendelyn Jones Warren, Ph.D.

Transgenic animal research is rapidly evolving to-ward practical and commercial applications. Two approaches for animal biotechnology include animals genetically engineered for "biopharming" and animals genetically engineered for improved agronomic traits. Biopharming, in general terms, applies not only to the harvesting of drugs, biologics, and industrial substances from milk, blood, or other tissues but also to animals engineered for tissue donation to humans, i.e., xenotransplantation. Animals with improved agronomic traits may exhibit increased feed efficiency and/or decreased time to market weights, animal disease resistance, or changes in the qualities of food derived from the animals. As stated in the White House Office of Science and Technology Policy Case Studies (available at *www.ostp.gov*), the FDA/CVM has proposed regulating transgenic animals under the "new animal drug" provisions of the Federal Food, Drug, and Cosmetic Act.

CVM scientists participated in a two-day workshop on transgenic animals, "Biotech in the Barnyard: Implications of Genetically Engineered Animals," as a means to interact with the interested public and to meet with leading researchers in the field. This multi-

Animals with improved agronomic traits may exhibit increased feed efficiency and/or decreased time to market weights, animal disease resistance, or changes in the qualities of food derived from the animals.

disciplinary workshop was sponsored by the Pew Initiative on Food and Biotechnology. In attendance were representatives from industry, academia, consumer groups, animal welfare groups, environmental groups, policy leaders and opinion makers. The transgenic animal workshop, held over two days (September 24-25) in Dallas, TX, was followed by the one-day symposium, co-sponsored by CVM, on animal cloning: "Animal Cloning and the Production of Food Products – Perspectives from the Food Chain." (The audio web cast recording of the both conferences can be accessed at *http://pewagbiotech.org/events/0924/*.)

The transgenic animal workshop was divided into four panels of three speakers each. At the completion of each panel, audience members were encouraged to ask questions of the panelists. It is worth noting that the panels were designed to have a mix of perspectives within each grouping. Additionally, after the completion of the day's panel discussion, all workshop participants were split into breakout groups for further exploration of the topics presented.

The first topic on the agenda was a review of the technology, "The ABCs of Transgenic Animals: Current and Future Applications," by Dr. Neal First. Dr. First's talk served as both a historical review of the field of transgenics and an overview of the scientific process of transgenesis. His talk noted the prevalent use of murine models in current biology labs and went on to discuss in detail efforts to bioengineer pigs lacking the 1,3 galactosyl transferase enzyme. This enzyme is responsible for the 1,3 galactosylated antigens which prohibit the successful xenotransplantation of swine organs to humans.

This opening talk led into the first panel on "Animal Matters: Social, Ethical and Animal Welfare Consideration." Participating in the panel were Drs. William Velander, Gary Comstock and Joy Mench. These three speakers individually and collectively addressed how transgenic technology fits with the public views on animals.

Dr. Velander's talk emphasized the human medical benefit of protein therapeutics made in genetically engineered animals. He emphasized the ability of researchers to produce prodigious amounts of human proteins in the mammary gland of a transgenic animal only during lactation so that it is naturally exported into the milk, just as any other milk protein. He noted that this process is typically not harmful to the host animal and yet can produce a complex protein suitable for human therapy. The specific example he cited was transgenic swine genetically engineered to produce Factor IX used in the treatment of hemophilia in humans.

Bioethicist Dr. Comstock spoke about what ethics should govern the treatment of transgenic farm animals. He suggested that while it was common to view

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. . . PEW INITIATIVE MEETING ON TRANSGENIC ANIMALS (Cont.)

transgenic animals as valuable production machines, it may be more beneficial to society that animals be viewed as beloved pets, which provide for sick humans and give us their lives in service. His take-home point was that transgenic animals are subjects of the scientists' own making and thus obligations to transgenic animals are greater than the obligations to those animals not subject to bioengineering techniques.

Dr. Mench discussed animal welfare issues. She noted that the lack of an animal welfare standard in conventional agriculture means there is no clear benchmark against which to measure the welfare of transgenic barnyard animals. This is even further complicated as many of the technologies used to create transgenic animals are also already used in conventional agriculture.

While the first panel discussed transgenic animals in the barn, the second panel discussed transgenic animals outside the barn. The second panel, "Beyond the Barn: Ecological and Human Health Considerations," was made up of three academicians, Drs. Bill Muir, Jim Murray, and John Coffin.

In discussing the ecological risk issues associated with transgenic animals, Dr. Muir argued that scientists could estimate the risk posed by a particular transgenic animal prior to release by analyzing the likelihood the transgenic animal could become established in the environment. This process includes evaluating four fitness components, such as fertility, fecundity, age of sexual maturity, and mating success.

Dr. Murray discussed food safety concerns related to transgenic animals. In addressing whether transgenic animals can inadvertently contain new food allergens and toxins, Dr. Murray stated that if the transgene is a totally new gene that has never been part of the diet, it should be carefully assessed. He stated that the magnitude of the food safety risk also depends on the process used to generate the transgenic animal. For instance, in animals created through microinjection, it is highly improbable that the insertion could activate the expression of a gene that produces a novel toxin or allergenic compound since only about 2% of an animal's DNA actually codes for genes.

Dr. Murray stated that if the transgene is a totally new gene that has never been part of the diet, it should be carefully assessed.

Dr. Coffin expanded the human safety discussion to include direct human health considerations. He noted that the use of transgenic farm animals poses some novel risks of infectious disease in humans depending on the technology used. Dr. Coffin noted the use of antibiotic resistance marker genes in the generation of transgenic animals may contribute to the reservoir of resistant pathogens. Additionally, if used to generate transgenic animals, viral vectors could potentially recombine with a latent virus buried in the animal's genome.

Dr. Coffin noted the use of antibiotic resistance marker genes in the generation of transgenic animals may contribute to the reservoir of resistant pathogens.

In presenting the potential impacts of transgenic animals on the environment and on humans, panelists emphasized the low risk and relative safety of transgenic animals especially if under Federal oversight.

While the first day addressed the impacts of transgenic animals inside and outside the barn, the second day moved to impacts of the technology in agricultural marketing and then finally to Federal oversight of the transgenic animals.

Dr. Cecil Forsberg led off the third panel of the workshop by presenting a case study on the economics and marketing of environmentally friendly transgenic pigs. Enviropigs, a specific type of transgenic pigs, produce manure that is lower in phosphorus and thereby cause less environmental pollution.

The consumer perspective on marketing transgenic animals was presented by Jean Halloran. She noted the divide between what scientists and industry are discussing and what the public is aware of and discussing. Ms. Halloran urged the FDA to educate the public on transgenic technology and to engage in continued public discussion on both legal and ethical issues.

Dr. Lawrence Schook explained how advances in genomics might be able to address many of the health, safety, and ethical concerns that have consumers

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. . . PEW INITIATIVE MEETING ON TRANSGENIC ANIMALS (Cont.)

worried. More sophisticated techniques will allow exact placement of the transgene into the DNA, mitigating the dangers of accidental gene activation or unintentional mutations caused by microinjection.

The final panel of the workshop provided an analysis of the laws and regulations governing the use of transgenic animals in the U.S. Presenting in the "Institutional and Legal Background" section were Fred Degnan, Michael Taylor, and Bud Locklear. A number of Federal regulatory agencies and statutes come into play when discussing transgenic animals. However, none of them specifically address transgenic animals since many regulations were enacted before technology had evolved to generate transgenic animals. All speakers noted that the predominant Federal agency involved in the oversight of transgenic animals was the Food and Drug Administration. Fred Degnan and Michael Taylor described, evaluated, and made recommendations regarding how the Agency can maintain the public's trust and ensure food safety, animal safety, and environmental safety.

In conclusion, the CVM scientists found the presentations and the workshop as a whole very informative. The presentations stimulated some lively discussions among the attendees. Through attending the meeting, the participating CVM scientists had a much stronger grasp of the concerns important to various stakeholders. This type of public interaction early in the regulatory process for transgenic animals will help regulatory scientists respond to stakeholders with understanding and ensure the best science-based decision process.

Dr. Warren is a pharmacologist with CVM's Division of Human Food Safety.

CVM ISSUES DRAFT GUIDANCE ON RAW MEAT DIETS

by Linda Grassie

FDA's Center for Veterinary Medicine (CVM) has issued for comment a draft guidance for industry entitled "Manufacture and Labeling of Raw Meat Diets for Companion and Captive Noncompanion Carnivores and Omnivores" (Guidance #122). This draft provides specific guidance on the manufacture and labeling of diets that contain raw meat, or other raw animal tissues, for consumption by dogs, cats, other companion or pet animals, and captive noncompanion animal carnivores and omnivores.

Draft Guidance #122 is posted on CVM's Home Page at: *http://www.fda.gov/cvm/guidance/published.htm#documents*. Single copies of the guidance may be obtained by writing to the *FDA Veterinarian*. Please send a self-addressed adhesive label to assist in processing your request.

FDA, and other agencies within the Department of Health and Human Services do not believe raw meat diets are consistent with the goal of protecting the public from significant health risks, particularly when such products are brought into the home and/or used to feed domestic pets.

Diets for carnivorous and omnivorous animals containing raw meat or other raw animal tissues have been on the market for many years for use by zoos, mink farms, dog racing facilities, and other professional establishments. Some of these products may have included meat and other tissues from mammals or poultry that have died other than from slaughter or have otherwise been unfit for human consumption. Products containing such tissues are adulterated under the Federal Food, Drug, and Cosmetic Act (FFDCA). However, a FDA Compliance Policy Guide

FDA, and other agencies within the Department of Health and Human Services, do not believe raw meat diets are consistent with the goal of protecting the public from significant health risks, particularly when such products are brought into the home and/or used to feed domestic pets.

(CPG 7126.23—*http://www.fda.gov/ora/compliance_ref/cpg/cpgvet/cpg690-500.html*) stipulates that investigation of such products should only be conducted as a follow-up to complaints or reports of injuries.

FDA presumes that when raw meat or raw animal tissues are purchased and used by zoos, mink farms, dog racing facilities, or other professional establishments,

(Continued, next page)

CVM ISSUES DRAFT GUIDANCE ON RAW MEAT DIETS (Cont.)

the purchaser is aware of the potential risks of using such products, from both a food safety and nutritional deficiency perspective. FDA also thinks that these purchasers can take measures to mitigate those risks. However, the new trend is toward use of raw meat diets for companion and captive noncompanion animals by owners who may not be as aware of the potential for harm.

Raw meat diets are often fed to working dogs, such as foxhounds and greyhounds.

Under current law, these products are classified as "foods" and do not require pre-marketing approval or certification. While objective data derived specifically from commercial raw meat pet foods are sparse; the potential for risk to public health from such products is undeniable given the microbiological results from studies of ingredients that could compose such products and the limited sampling of commercial raw pet foods. Therefore, FDA believes that specific guidance for industry is warranted for how such products could be manufactured and labeled in order to protect pet owners and pets from risks involving food safety and nutritional deficiency.

In addition to bacterial contamination issues, the draft guidance warns about the dangers of dental or gastrointestinal trauma when bone is included in other than ground form. It also recommends measures to minimize contamination and disease transmission through the use of irradiation, proper transport and storage of product by manufacturers, distributors, and retailers; participation in USDA's voluntary inspection program; and the development and implementation of a Hazard Analysis and Critical Control Point program by manufacturers.

This guidance represents the Agency's current thinking on these products. It does not create or confer any rights for or on any person and does not operate to bind the FDA or the public. An alternate approach may be used as long as it satisfies the requirements of applicable statutes and regulations.

Comments and suggestions regarding this document should be sent to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5600 Fishers Lane, Room 1061, Rockville, MD 20852. All comments should be identified with the Docket No. 02D-0468.

Additional information about the guidance may be found in the December 18, 2002, **(***http://www.fda.gov/OHRMS/DOCKETS/98fr/02-31721.htm***)** *Federal Register*, and from Dr. William J. Burkholder, Division of Animal Feeds, (HFV-228), Center for Veterinary Medicine, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-0179 (email: *bburkhol@cvm.fda.gov*).

Linda Grassie is Deputy Director of CVM's Communications Staff.

CONSENT DECREE SIGNED

On December 13, 2002, a Consent Decree of Permanent Injunction was signed in U.S. District Court for the Southern District of Florida against Larson Dairy, Inc. and Louis E. Larson, Sr. for the sale of cows and calves for human consumption whose tissues exceeded the tolerances for residues of penicillin and neomycin. The violative tissue samples from Larson Dairy were collected from November 17, 2000 through October 15, 2001. Larson Dairy is the largest dairy in the State of Florida producing over 30,000 gallons of milk a day and shipping for human consumption over 6,000 head of cattle a year.

JEROME G. WOYSHNER SELECTED AS CHAIRMAN OF THE CVM FIELD COMMITTEE

Jerome Woyshner, Director of FDA's New York District Office, has been chosen to replace retiring Ballard Graham as Chairman of the CVM Field Committee.

Mr. Woyshner is a native of Lackawanna, NY, and began his career with FDA in 1964 as an investigator in the Buffalo District Office. He subsequently relocated to the Pittsburgh Resident Post and the New York District offices where he also served as investigator. He was promoted to a supervisory investigator position in 1972 and to the Director of Investigations Branch position in 1982. In 1998, the Buffalo and New York District Offices merged and he assumed statewide responsibility as the Director of Investigations Branch.

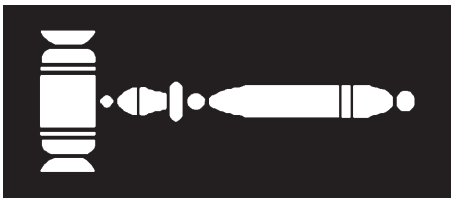
Jerome G. Woyshner

Mr. Woyshner is a graduate of West Virginia University and attended graduate school at Syracuse University. He has been the recipient of the FDA Award of Merit, Commendable Service Award, PHS Public Service Award, and Vice President Gore's Hammer Award.

FDA Field Committees meet routinely with Center representatives and serve as the principal contact for the Office of Regulatory Affairs (Field and Headquarters) to address program priorities or modifications, special assignments, resource utilization, and significant issues of concern to either party. This type of partnering offers a key mechanism in FDA's efforts to optimize consumer protection in carrying out its mission. In addition, Committee members act as liaisons with State agencies who play key roles in the enforcement of FDA's regulations. Other CVM Field Committee members include Brenda Holman, RFDD, Pacific Region; Thomas Gardine, District Director, Philadelphia District; Dennis Linsley, District Director, San Francisco District; Gayle Lancette, Director Southeast Regional Laboratory; Austin R. Long, Director, Pacific Regional Laborarory-Northwest; Charles Sedgwick, District Director, Kansas City District and; Howard Lewis, Director, Nashville Branch, New Orleans District.

REGULATORY ACTIVITIES

by Karen A. Kandra



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

- Luis M. Bettencourt, Owner, Bettencourt Dairies, Wendell, ID
- Kendall S. Cody, Owner, Cazenovia, NY
- Steve X. Simas, Managing Partner, Lu-Ar Dairy, Hanford, CA

The above violations involved illegal residues of penicillin and sulfadimethoxine in cows; and gentamicin in a cull dairy cow.

A warning letter was issued to Alton J. Hall, D.V.M., President, Natchez Animal Supply Company, Natchez, MS, for significant deviations from Current Good Manufacturing Practice regulations (CGMP) Title 21, *Code of Federal Regulations*, Part 211, in conjunction with the firm's aquaculture drug repackaging operations, causing the firm's drug, Formalin-F (formaldehyde), to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

A warning letter was issued to John H. Tyson, CEO, Tyson Foods, Inc., Springdale, AR, for significant deviations from the Current Good Manufacturing Practice (CGMP) regulations for Medicated Feeds (Title 21 *Code of Federal Regulations*, Part 225). Such deviations included but are not limited to failure to maintain an accurate daily inventory record for each drug used; failure to investigate and implement corrective action for significant discrepancies between actual drug usage and theoretical drug usage; failure to investigate corrective action when production records document the manufacture and shipment of super potent medicated feed; and failure to flush all manufacturing equipment and failure to ensure that the amount of flush material used is adequate to prevent cross-contamination.

A warning letter was issued to Ronald A. Christensen, President and General Manager, Sunnymead Ranch, Inc., Idalou, TX, for significant deviations from the

(Continued, bottom of next page)

FDA REVISES DEFINITION OF THE TERM "NO RESIDUE"

FDA has published a final rule that revises the definition of "no residue" in the new animal drug regulations to mean that no residue is detected with an approved regulatory method. This means that any residue in the target tissue must be non-detectable or below the limit of detection (LOD) of the approved regulatory method. Under the regulation, FDA has defined the LOD of an analytical method as the lowest concentration of analyte (the chemical that is detected and measured by the analytical method) that can be confirmed by the approved regulatory method. FDA published this final rule in the December 23, 2002, *Federal Register* (*http://www.fda.gov/OHRMS/DOCKETS/98fr/02-32216.htm*).

FDA promulgated "Regulation of Carcinogenic Compounds Used in Food-Producing Animals" on December 31, 1987 (Title 21, Parts 500.80 – 500.92 of the *Code of Federal Regulations*). In the regulation, informally referred to as the Sensitivity of the Method (SOM) regulation, FDA provided an operational definition of "no residue" and identified the steps a sponsor of a carcinogenic compound should follow to secure approval of the compound. The regulation implemented the "DES proviso" of the Delaney Clause to the Federal Food, Drug, and Cosmetic Act. This permits the approval of a new animal drug that induces cancer if "no residue" will be found, by methods prescribed or approved by the Secretary, in edible tissues of treated animals.

FDA is revising this definition in response to a 1995 legal opinion issued by the Department of Justice (DOJ), Office of Legal Counsel, which concluded that this operational definition of "no residue" is not legally supportable. However, the DOJ stated that FDA may use the "no significant risk" level as a benchmark for rejecting analytical methods.

Many other key aspects of the regulation (21 CFR 500.80-500.92 — *http://www.access.gpo.gov/nara/cfr/waisidx_02/21cfr500_02.html*) remain the same: the "no significant risk" level will still be determined according to established procedures; the concentration of marker residue that the regulatory method must be capable of measuring in the target tissue (Rm) will still be calculated; the method will still be validated to at least Rm; but, FDA will use submitted data on the method to determine the LOD. Consequently, the data necessary to meet the requirements of the new rule are identical, or nearly identical, to those previously delineated. Moreover, the revision of the definition of "no residue" preserves the same level of public health protection.

This final rule is effective January 22, 2003. Additional information on the final rule may be found in the December 23, 2002, *Federal Register* and from Dr. Steven D. Brynes, Center for Veterinary Medicine (HFV-151), Division of Human Food Safety, Food and Drug Administration, 7500 Standish Place, Rockville, MD 20855, 301-827-6975.

REGULATORY ACTIVITIES (Continued)

requirements set forth in Title 21, *Code of Federal Regulations*, Part 589.2000 – Animal Proteins Prohibited in Ruminant Feed. This regulation is intended to prevent the establishment and amplification of Bovine Spongiform Encephalopathy. The inspection revealed that the firm manufactures feed for sheep that may contain residues of prohibited material. The sheep feed is mixed in the same equipment that is used for mixing chicken feed containing bovine meat and bone meal. Sheep consuming this feed are ultimately auctioned for sale as food for human consumption.

CVM COMINGS AND GOINGS

In an effort to keep our readers apprised of new personnel developments, we will report new hires, retirements, and resignations of CVM personnel.

NOVEMBER HIRES

- Dr. Linda Benjamin/Chemist/OSC
- Dr. John Harshman/Staff Fellow/ONADE
- Eve Princler/Training Specialist/OM
- Sherri Washington/Training Specialist/OM

DECEMBER HIRES

- Dr. Bernadette M. Dunham/Deputy Director/ONADE

RETIREMENTS

- Dr. Patricia Leinbach/ONADE
- Dr. Thomas McKay/ONADE

SCIENTISTS GATHER FOR NARMS SCIENTIFIC MEETING

by Joanne M. Kla, Marcia L. Headrick, D.V.M., M.P.H. and Paula J. Fedorka-Cray, Ph.D.

Organizers of the NARMS program used their most recent regularly scheduled Scientific Meeting to present information about how the program works including where samples come from, how are they processed and how bacteria are tested for antimicrobial susceptibility. Among other topics, scientists discussed laboratory culture technique challenges and phenomena that have been observed in the NARMS testing laboratories.

The NARMS program was created in 1996 to discover whether bacteria found in animals are developing resistance to antimicrobial drugs, and whether those resistant bacteria are making people ill.

At the most recent meeting, held in November, scientists from the Centers for Disease Control and Prevention (CDC) provided information on the collection and susceptibility testing of human *Salmonella*, *Shigella*, *E. coli*, *Campylobacter*, *Listeria* and *Enterococci*, as well as analysis and reporting methods.

Researchers from the United States Department of Agriculture (USDA) provided information on on-going activities related to the animal arm of NARMS. Food Safety Inspection Service (FSIS) collects samples at slaughter plants for testing, Agricultural Research Service (ARS) has several sentinel sites and also collects on-farm samples. Animal and Plant Health Inspection service (APHIS) contributes samples collected through the National Animal Health Monitoring System (NAHMS) program. The Antimicrobial Resistance Research Unit of USDA cultures these samples for organisms of interest and tests their antimicrobial susceptibility using the same panel of antimicrobial drugs as CDC and CVM.

CVM scientists presented information on the retail arm of NARMS, including a presentation on the Iowa Retail Meat Study conducted by FDA, CVM, Division of Epidemiology and CVM's Office of Research. The Iowa Pilot study, part of a planned expansion of the NARMS program, was an epidemiological effort to compare bacteria found on retail meats to bacteria isolated from humans, to see if there is a link in terms of prevalence and antimicrobial resistance. This pilot study provided useful information on conducting a retail study, including study design and sampling methods. The researchers found that the Iowa Pilot study was a good model on which to base the expanded FoodNet Retail Meat Study.

FDA researchers also presented information on a new addition to the retail arm of NARMS, the FoodNet Retail Meat Study, currently being conducted by CVM, Division of Epidemiology and Office of Research in collaboration with the CDC FoodNet Sites.

Participants reported on culture challenges presented by *Salmonella*, *Shigella*, *E.coli*, *Campylobacter*, *Enterococci*. They also shared information on enhancements their laboratories have developed to increase isolation of *Campylobacter*, typically a difficult organism to isolate in the laboratory.

CVM scientists presented information on the retail arm of NARMS, including a presentation on the Iowa Retail Meat Study conducted by FDA, CVM, Division of Epidemiology and CVM's Office of Research.

The participants also heard information about surveillance programs in other parts of the world, with presentations about zoonotic pathogen and antimicrobial resistance monitoring systems in Canada and Italy, and the WHO Global Salm-Surv program (an international *Salmonella* surveillance network that includes the World Health Organization, the Danish Veterinary Service, CDC, Health Canada, and Institut Pasteur).

CAHFSE

Another program discussed at the meeting was a new USDA program: *Collaboration on Animal Health, Food Safety, and Epidemiology* (CAHFSE). This program is an outgrowth of Agricultural Research Service (ARS), FSIS, and APHIS/NAHMS collaborations dating back to 1992. The CAHFSE program, which is scheduled to start in 2003, will have APHIS, ARS and FSIS as equal partners.

This new surveillance system will be patterned after NAHMS, focused on animal health and public health issues that will include data collected at slaughter. Pork will be the first commodity examined in the program. The program will conduct quarterly sampling at 25

(Continued, next page)

SCIENTISTS GATHER FOR NARMS SCIENTIFIC MEETING (Cont.)

operations, with 75 samples per operation. Samples will be sent to the ARS, Antimicrobial Resistance Research Unit (ARRU) laboratory for culture of *Salmonella*, *Campylobacter*, *E. coli*, *Enterococci,* and other organisms of interest.

In addition to the laboratory work, they plan to conduct risk analyses, epidemiologic studies and field investigations to describe environmental conditions at the sample collection sites. Anticipated benefits and outcomes include providing science-based answers to questions including what impact antimicrobial drug use may have on animal and human health.

The NARMS program plays an important role in the overall understanding of antimicrobial drug resistance. The primary role of NARMS is to provide descriptive data on the extent and temporal trends in antimicrobial susceptibility in *Salmonella* and other enteric organisms from human and animal populations.

Additionally, NARMS facilitates the identification of resistance in humans and animals as it arises, provides information on antimicrobial resistance to veterinarians and physicians, prolongs the life span of approved drugs by promoting the prudent and judicious use of antimicrobial drugs, and identifies areas

The primary role of NARMS is to provide descriptive data on the extent and temporal trends in antimicrobial susceptibility in* Salmonella *and other enteric organisms from human and animal populations.

for more detailed investigation. NARMS also aids in antimicrobial resistance research by providing a national source of enteric bacterial isolates that may be invaluable for research such as diagnostic test development, discovering new genes and molecular mechanisms associated with resistance, studying mobile gene elements, and for virulence and colonization studies.

For more information on the NARMS program, please contact Dr. Marcia Headrick of FDA, CVM via e-mail at mheadric@cvm.fda.gov, or call (706) 546-3689. Additional information on the NARMS program is also available on the CVM NARMS web page at http://www.fda.gov/cvm/index/narms/narms_pg.html . A brochure on the NARMS program is available by contacting the *FDA Veterinarian* at (301) 827-3800.

Joanne Kla is a Consumer Officer on the Communications Staff and Assistant Editor of the FDA Veterinarian. Dr. Headrick is an Epidemiologist with CVM's Division of Epidemiology stationed in Athens, Georgia and the FDA/CVM NARMS Coordinator. Dr. Fedorka-Cray is Research Leader with USDA's Antimicrobial Resistance Research Unit in Athens, Georgia.

REGISTER NOW FOR THE FDA SCIENCE FORUM

Don't miss the 9th Annual FDA Science Forum, "FDA Science: Protecting America's Health." This premiere scientific event will be held April 24-25, 2003, at the new Washington Convention Center. The Science Forum, FDA's annual showcase of scientific achievements, is an excellent opportunity to see the role science plays in our regulatory mission and to discuss new scientific trends and regulatory challenges.

Open to the public, the 2003 Forum is designed to bring FDA scientists together with representatives from industry, academia, government agencies, consumers groups, and international constituents to explore emerging public health issues and to learn and share knowledge and ideas about the science-based mission of the Agency.

Speakers and panelists will address emerging issues in risk management and assessment, public health initiatives in the aftermath of the September 11, 2001, terrorist attack, and novel FDA science initiatives.

A poster session featuring all areas of FDA regulatory science will be presented to provide an opportunity for interested scientists to engage in information exchange with FDA scientists. Additionally, this forum hosts its first full exposition of scientific products and technologies. While on-site registration will be available, seating will be limited. So register soon!

For more information on primary scientific topics, speakers, etc., please visit: *www.dcscienceforum.org*.

INTERNATIONAL ACTIVITIES

On December 20, 2002, a group of visitors from Hebei and Jiangxi Provinces in the People's Republic of China met with CVM's international, GMP, and compliance staffs to be briefed on CVM regulatory programs. CVM believes it is valuable to exchange information with other countries concerning the policies and procedures that FDA uses to regulate products. Each year CVM receives approximately 40 groups of foreign visitors who discuss a variety of topics, including the Center's organization, regulatory processes, research programs, and new initiatives. These visitors return to their countries with a greater understanding of health and regulatory issues and approaches in the United States, the Center's role as a public health protection agency, and what is needed to meet FDA's requirements.

Photo by Linda Grassie

Back row: *Visitors Wu Li-Ming and Liu Xu Dong, CVMers Dennis Bensley and Geoffrey Wong*
Front row: *Visitors Sun Xiao Fang, Zhao Yong Ping, and Zhang Zhimin, CVMers Bill Marnane, Mai Huynh, Merton Smith, and Kim Young*

CVM SCIENTISTS HELP RESOLVE RUSSIA-U.S. TRADE DISPUTE ON POULTRY

by Steven D. Brynes, Ph.D. and Nicholas E. Weber, Ph.D.

Two Center for Veterinary Medicine (CVM) scientists, Dr. Nicholas Weber and Dr. Steven Brynes, both of the Office of New Animal Drug Evaluation, played key roles in the resolution of last year's trade dispute with Russia over the export of poultry from the United States. At the request of Secretary of Agriculture Ann Veneman and as part of CVM's responsibility to communicate the scientific basis for its regulatory requirements, both scientists served on U.S. Government negotiation teams as technical experts on human food safety, particularly drug residues. The teams also included representatives from USDA's Foreign Agricultural Service, Food Safety and Inspection Service, and Animal and Plant Health Inspection Service, and the U.S. Trade Representative's Office.

On March 10, 2002, Russia imposed a temporary import ban on U.S. poultry. The measure created a significant crisis for U.S. poultry and poultry products. The Russian market is very important to U.S. poultry meat producers, accounting for approximately $600 million in exports annually, and the ban quickly caused serious economic damage in many poultry-growing regions of the U.S.

From the U.S. perspective, there was no justification for the ban. All U.S. poultry exports were certified

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. . . TRADE DISPUTE ON POULTRY (Continued)

to be in compliance with Russia's export veterinary certificate that had been agreed to in 1996. USDA argued that all U.S. poultry that bears the USDA mark of inspection was subject to every aspect of U.S. regulations and was, therefore, safe, wholesome and properly handled. It is the same poultry that U.S. consumers purchase.

Seeking to resolve the issue, Russia agreed to receive a U.S. delegation, which included Dr. Weber, on short notice. During the talks, differences in legislative and regulatory frameworks for food safety were examined. Both sides reached an understanding of the need to begin drafting a new agreement (i.e., on the veterinary certificate) that would regulate U.S. poultry exports to Russia. As a result of the talks, on March 31, 2002, Russia agreed to lift the temporary ban before April 10, 2002, provided the U.S. complied with certain prescribed remedial actions.

The Russian market is very important to U.S. poultry meat producers, accounting for approximately $600 million in exports annually . . . .

On April 30, 2002, Russia sent a draft new veterinary certificate to the U.S. The veterinary certificate, to which U.S. producers must adhere, covers a wide range of controls designed to ensure a wholesome product. These controls apply to, among others, the areas of processing and packaging, labeling, transit countries, infectious diseases, antibiotic and hormone usage, drug and heavy metal residues, and preservation.

On May 14, 2002, Ann Veneman, Secretary of USDA, acting at the direction of President Bush, wrote to her counterpart Alexander Gordeyev, Deputy Prime Minister of Agriculture, urging that negotiations begin to allow agreement on a new veterinary certificate within 60 days. To this end, on May 22, 2002, Deputy Prime Minister Gordeyev advised Ms. Veneman that a Russian team would arrive in Washington, DC, in late May or early June.

The second round of negotiations ran from June 8 to June 13, 2002. Drs. Weber and Brynes participated in these talks during which they (1) presented an overview on the human food safety assessment of veterinary drug residues and (2) attempted to gain clarification on Russian safety concerns and to obtain more information as to which drugs are actually approved for use in poultry in Russia. Dr. William Price of CVM's Office of Surveillance and Compliance attended these talks as well and addressed the issue of genetically modified (GMO) feeds. Dr. Price and Dr. Thomas Moskal had also been involved prior to March in preparing responses to earlier written questions from Russia.

Generally, these negotiations, tense and at times combative, yielded no major breakthroughs. However, as the negotiations were drawing to a close, the CVMers proposed written revisions to those sections of the April 30, 2002, veterinary certificate dealing with the use of veterinary drugs in poultry.

Following the Washington talks, Russia invited an expert team to Moscow to continue the negotiations. Indicative of just how important the negotiations were deemed, the National Security Council (NSC) requested a meeting with the U.S. team prior to its departure for Moscow. NSC suggested negotiation strategy and urged the team to negotiate well on behalf of the U.S. Government and the U.S. poultry industry.

Dr. Brynes served on the 11-person team that visited Moscow from June 24 to July 3, 2002. The Moscow talks were intense, with both sides clearly committed to realizing an agreement. Although a great deal was achieved, it became clear that agreement on a new certificate would not be accomplished by July 3. On July 2, therefore, Dr. Brynes helped compose a letter to Sergey Dankvert, First Deputy Minister of Agriculture, that might mitigate the Russians' concerns regarding the United States' use of hormones and antibiotics and of residues.

On August 23, 2002, Agriculture Secretary Ann M. Veneman, Commerce Secretary Donald L. Evans and U.S. Trade Representative Robert B. Zoellick announced that the long-running poultry trade dispute between the United States and Russia had been resolved. Both sides agreed to a new veterinary certificate that would allow for the continuation of U.S. poultry exports to Russia. In their announcement they commended the extraordinary efforts of all members of the U.S. negotiating team and expressed

(Continued, next page)

. . . TRADE DISPUTE ON POULTRY (Continued)

appreciation for the support they received from members of Congress.

The agreement on a new veterinary certificate notwithstanding, there remained some problem areas between Russia and the U.S., especially concerning the use of tetracyclines in poultry. The Russian muscle tolerance for drugs of the tetracycline group is 10 parts per billion (ppb), at least two orders of magnitude less than that in the United States (2 parts per million). It was suggested that a way around the issue could be to determine conditions of use that would permit U.S. producers to comply with the Russian tolerance of 10 ppb.

At the end of August, USDA invited Drs. Weber and Brynes to join the Tetracycline Task Group which included USDA and poultry industry representatives. The goal of the group was to plan a research program that would allow exported poultry products (legs and deboned meat) to comply with the 10 ppb tetracycline tolerance. Drs. Weber and Brynes continue to provide guidance to USDA and the poultry industry on the research project, which appears to be moving forward smoothly.

Drs. Brynes and Weber are senior regulatory review scientists in CVM's Office of New Animal Drug Evaluation.

NEW ANIMAL DRUG APPROVALS

Company	*Generic and (Brand) Names*	*Indications*	*Routes/Remarks*
Novartis Animal Health US, Inc. (NADA 141-203)	Deracoxib (Deramaxx™) RX	Dogs. For control of postoperative pain and inflammation associated with orthopedic surgery.	**ORAL**—The NADA provides for the veterinary prescription use of Deramaxx tablets for the control of postoperative pain and inflammation associated with orthopedic surgery in dogs weighing four or more pounds. *Federal Register* 11/13/02
Purina Mills, Inc. (NADA 141-171)	Lasalocid (Bovatec 68)	Pasture cattle. For increased rate of weight gain.	**MEDICATED FEED**—The NADA provides for the use of a lasalocid Type A medicated article to make free-choice Type C medicated feed mineral blocks used for increased rate of weight gain in pasture cattle (slaughter, stocker, feeder cattle, and dairy and beef replacement heifers). *Federal Register* 12/05/02
Elanco Animal Health A Division of Eli Lilly & Co. (NADA 141-198)	Salinomycin (Bio-cox), Tylosin (Tylan)	Broiler chickens. For use as an aid in prevention of coccidiosis, and for increased rate of weight gain and improved feed efficiency.	**MEDICATED FEED**—The NADA provides for use of approved, single-ingredient salinomycin and tylosin phosphate Type A medicated articles to make two-way combination Type C medicated feeds used as an aid in the prevention of coccidiosis caused by *Eimeria tenella*, *E. necatrix*, *E. acervulina, E. maxima, E. brunetti*, and *E. mivati*, and for increased rate of weight gain and improved feed efficiency in broiler chickens. *Federal Register* 12/05/02

SUPPLEMENTAL NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Alpharma, Inc. (NADA 39-417)	Decoquinate (Deccox)	Cattle, sheep, goats. For the prevention of coccidiosis.	**MEDICATED FEED**—The supplemental NADA provides for the use of decoquinate medicated articles to make Type C medicated feeds for cattle, sheep, and goats at a broader range of concentrations for the prevention of coccidiosis caused by various *Eimeria* species. *Federal Register* 12/05/02
Elanco Animal Health A Division of Eli Lilly & Co. (NADA 140-929)	Tilmicosin (Micotil® 300) RX	Sheep and cattle. For the treatment of ovine respiratory disease.	**SUBCUTANEOUS**—The supplemental NADA provides for subcutaneous injection of tilmicosin phosphate solution for the treatment of ovine respiratory disease (ORD). FDA is also amending the regulations to add tolerances for residues of tilmicosin in sheep muscle and liver and in cattle muscle. *Federal Register* 12/05/02

ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Phoenix Scientific, Inc. (ANADA 200-069)	Gonadorelin Diacetate Tetrahydrate (Fertelin) RX	Dairy cattle. For the treatment of ovarian cysts.	**INTRAMUSCULAR OR INTRAVENOUS**—The product Fertelin approved under this ANADA is a generic copy of Merial, Ltd.'s Cystorelin, approved under NADA 98-379. *Federal Register:*11/13/02
Norbrook Laboratories, Ltd. (ANADA 200-306)	Oxytetracycline	Cattle and swine. For the treatment of various bacterial diseases.	**INTRAMUSCULAR OR SUBCUTANEOUS**—The product Oxytetracycline Injection approved under this ANADA is a generic copy of Pfizer's LIQUAMYCIN LA-200 approved under NADA 113-232. *Federal Register* 12/05/02

SUPPLEMENTAL ABBREVIATED NEW ANIMAL DRUG APPROVALS

Company	Generic and (Brand) Names	Indications	Routes/Remarks
Pennfield Oil Co. (ANADA 200-154)	Oxytetracycline (Pennox 200)	Dairy cattle and swine. For the treatment of various bacterial diseases.	**INTRAMUSCULAR OR SUBCUTANEOUS**—The supplement provides for the administration of this oxytetracycline injectable solution to lactating dairy cattle. *Federal Register* 12/05/02

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