REPORT OF THE COMMITTEE ON BIOLOGICS AND BIOTECHNOLOGY

Chair: Robert W. Tully, Lenexa, KS
Vice Chair: Charles A. Mihaliak, Indianapolis, IN

Joan M. Arnoldi, WI; Charles A. Baldwin, GA; Karen E. Burns-Grogan, GA; Yung Fu Chang, NY; James J. England, ID; William H. Fales, MO; Robert W. Fulton, OK; Joe S. Gloyd, DE; Keith N. Haffer, SD; Larry L. Hawkins, MO; Rudolf G. Hein, DE; Richard E. Hill, IA; Joe N. Huff, CO; Majon Huff, CO; Robert F. Kahrs, FL; Terry Klick, OH; Hiram N. Lasher, DE; Lloyd H. Lauerman, WA; John C.. Lawrence, ME; Randall L. Levings, IA; Bob E. Pitts, GA; Deepanker Tewari, PA; Deoki N. Tripathy, IL; Lawrence Williamson, IN.

The Committee met during the annual meeting on Monday October 16, 2006 at 7:00 p.m. The Chair welcomed the participants to the Minneapolis Hilton Hotel, Minneapolis, Minnesota. Seven members, twelve new members and sixteen attendees were present. Last year's committee report and the agenda for the meeting were reviewed and attendees introduced themselves.

Bob Tully called the Committee to order: The Chair announced that Vice-Chair Chuck Mihaliak was unable to attend due to business commitments. The meeting this year is on Monday evening and the chair expressed pleasure with the large interest and turnout.

The Committee had everyone introduce themselves. The Chair read the mission statement and reiterated the reason for our Committee and the responsibility to the industry. The Chair explained the Committee action process of resolution formation and the ways that our committee takes action by either submitting resolutions to the United States Animal Health Association (USAHA) or secondly and less formally through recommendation to the USAHA President.

The roster for attendance was passed and all encouraged to list their membership status and encouraged all to join and become involved. The Committee mission statement is as follows.

"The purpose of the Committee on Biologics and Biotechnology is to monitor 1) new development in veterinary biologics, 2) regulation of the manufacture, distribution and use of veterinary biologics, and 3) needs of the livestock industries for new biological products. The Committee has the responsibility of keeping abreast and advising USAHA of new biotechnology, products and regulations that may have profound economic implications on animal health. Further, the Committee provides a forum to focus on issues and developments in the field of biotechnology that are designed to provide protection to man, animals and the environment."

Richard Hill, Director, Center for Veterinary Biologics (CVB), Veterinary Services (VS), Animal and Plant Health Inspection Service (APHIS), U.S. Department of Agriculture (USDA), reviewed and highlighted a number of activities that have occurred at CVB over the last year. He indicated to the group that the 2005 United States Animal Health Report is now available on the web. Hill provided an update on the National Centers for Animal Health. The Ames Laboratory Modernization Plan Brings three animal health institutes together in one site: the CVB; National

Animal Disease Center, Research (NADC); and the National Veterinary Services Laboratories (NVSL). The Plan calls for the modernization and consolidation of facilities from existing 2002 level programs. The Combined Services Plan, announced September 2005, provides for 286 support positions assigned to APHIS and Agriculture Research Service (ARS). All existing buildings are currently in use except for two. Tear-down will continue old NADC facilities and some animal housing facilities. Additionally, there is no funding for equipment or operational expenses.

Dr Hill then spoke about Veterinary Services Current and Emerging Issues, noting key VS leadership changes, including: Dr. Larry Granger, Director of the Center for Epidemiology and Animal Health (CEAH); Dr. Jose Diez, Associate Director of Emergency Management and Disease (EM&D), Dr. Beth Lautner, Director of the NVSL; Glen Garris, VS; Brian McClusky, National Surveillance Unit (NSU), Barb Martin, National Animal Health Laboratory Network (NAHLN); and Larry Elsken, Global Vaccine Manager. Hill also discussed vaccine discontinuance, referencing the brucellosis and psuedorabies eradication, and related white paper posted on the web site. APHIS will continue to allow vaccine production for export following eradication.

CVB Activity Summary

- Submissions -- 6,646
- Product Licenses and Permits Issued – 76
- Unique Products Licensed – 11
- Serials Released – 15,945
- % Serial Tested – 8.46%
- Inspections – 85
- Investigations – 53

CVB continues operating under continuing resolution. Without additional funding expect dramatic changes to system and scope of activities. Currently, there are 25 personnel vacancies at CVB. Incremental operating costs for CVB's share of the new National Center for Animal Health are significant. Hill then presented the current organizational chart for CVB. CVB will host a public meeting, its 14th, on March 28-29, 2007 in Ames, Iowa.

Byron Rippke, Director of CVB, Policy, Evaluation and Licensing (PEL), shared the following information with the committee in regards to the agency's activities. He noted the PEL organization chart, including: Larry Elsken, re-assigned to Global Vaccine Manager; Scott Taylor, transferred to Inspection and Compliance (IC) as Biologic Specialist; the biometrics staff is currently fully staffed, as well as noting six shared staff, two with USDA, Agriculture Research Service, two NVSL and two CVB. The PEL 2007 priority activities include laboratory testing, program documentation (policy), and Program Quality Assurance. PEL Program published documents for 2006 include 22 CVB notices, four VS Memorandums, and 10 documents posted to Web site for comment. Additionally, the following draft documents are in progress: test exemptions for detection of extraneous avian leucosis; availability of *Leptospira grippo* and *ictero* standards; policy regarding rabies vaccine; testing designations; and guidance for designing, interpreting, and reporting inactivation studies. In 2006, there were 97 total licensees (three new in 2006) and 22 total permittees (two new in 2006).

Dr Rippke presented summary graphs of the following PEL licensing data (contact his office for copies): number of biotech products licensed over time; number of biotech products licensed by category (1, 2 and 3); number of diagnostic products licensed over time; number of products licensed over time; number of FFM products licensed over time; number of biologic permits issued over time; and number of aquaculture products licensed over time. Dr. Rippke also stated that Influenza would be the topic at the March 2007 public meeting (including equine and canine influenza.

Mr. Steven Karli reported CVB-IC fiscal year 2006 activities. CVB-IC monitors over 135 active licensees and permittees at nearly 175 sites globally. CVB conducted 38 in-depth inspections, three follow-up inspections and 44 special inspections. The majority of special inspections were conducted for product or facilities inspections and also to conduct inspections for the VS National Center for Import and Export for compliance to the Select Agent regulations as part of the registration process under the Agriculture Bioterrorism and Preparedness Act of 2002.

In August, the consolidation of Information Management unit was initiated as a support services for the National Center's for Animal Health. This unit reports to the Director of Inspection and Compliance and includes information technology, library and visual services for NVSL, National Animal Disease Center and CVB. Full implementation of the unit is targeted to be completed by February 2007. On September 1, 2006, the Information Management Resource Services unit came under CVB supervision and direction. This unit, previously reporting to the Director of NVSL, included all of the APHIS information technology support for the Ames campus.

In addition, budget resources for fiscal year 2007 continue to be limited. As a result, CVB is implementing a plan to shift resources (human and financial) to priority areas identified by the Center Directors. Inspections and quality assurance continue to be priorities for the unit.

In Fiscal Year 2006, CVB processed 456 requests for Export Certificates (serial) and in excess of 2834 Certificates of Licensing and Inspection (product). Export activities by serial increased by nearly 25% this year and export activities by product increased by approximately 5% from FY 2005 levels. These numbers still represent overall reductions in product exports primarily due to the report of Bovine Spongiform Encephalopathy in the United States. Serials reviewed and processed by CVB were reported and summarized as 16,655; 15,945 serials were released for marketing – representing nearly stable numbers since FY 2003. Administrative Inspection Reviews continued in FY2006 and was expanded to include permittees as well. CVB sent out 65 reviews and processed 49 of those reviews. This new inspection process has provided CVB with a means to work with licensed manufacturers outside of the normal inspection process to assure CVB files are current as well as providing manufacturers with the opportunity to schedule their resource utilization to make sure their regulatory files are kept current.

The CVB Directors have continued their commitment to a Quality Management System. In FY 2006, all employees received training specific to the ISO 9001 and ISO 17025 standards. In addition, CVB Inspectors also received specific training for auditing guidelines (ISO 19011) in March 2006. CVB continued it's commitment to process improvement by conducting process audits to further improve internal processes for both CVB Inspection and Compliance, and the Policy, Evaluation and Licensing units. CVB has also contracted with an ISO Registrar for ISO 9001 Registration to be completed in fiscal year 2007.

Compliance activities reported included updates on investigation numbers for CVB (50 opened, 17 closed). Investigations opened included false and misleading advertising, promotions and/or product labeling. Additional compliance issues facing CVB in 2007 are continuing to look at our regulations to determine changes as a result of lesson's learned from previous investigations/cases. Also, CVB is working collaboratively with the California Department of Food and Agriculture to take a comprehensive look at those firms that operate under the California exempted program. An update on pharmacovigilance activities was also provided and progress within VICH continues. The expert working group met two times this fiscal year and have been able to make progress on documents. See the VICH website for specific documents and their status. Voluntary reports of adverse events continue to be received by the CVB and a summary of the types of reports was published in the October 1, 2006, issue of the Journal of the American Veterinary Medical Association.

Discussion

Issues from the floor included a status report on the 2004 Resolution 13 regarding publication of rule making authorizing the use of gamma irradiation for the importation of commercial shipments of fetal bovine serum from countries and/or regions that are free of BSE, but having restrictions because of other pathogens that can be eliminated by gamma irradiation. In 2005 the committee made further "recommendations" on two measures for the agency to consider in the re-proposal. Representatives from NCIE were present at the 2006 committee meeting and stated there was no change as the proposal was in progress and the risk analysis and regulatory work plan have been drafted. NCIE reported that the proposal was not assigned a "level 1" proposal.

Extensive discussion was held regarding the perceived need additional funding CVB. The agency is currently operating under a continuing resolution. The budget for CVB has been basically flat for 3 years and if continued the leadership at CVB reported there would be a drastic change in the scope of activities.

This discussion resulted in a motion by Bruce Addison and second by Bob Tully to draft a resolution that the agencies budget of $19 million be fully funded as requested by the agency. The vote on the resolution was unanimous in favor.

Scientific Presentation

North American Reference Tuberculin Project

Joan M. Arnoldi
Project Coordinator

The purpose of the current project is to compare the purified protein derivatives (PPDs) used for skin testing of cattle in tuberculosis eradication programs in North America (Canada, Mexico, and the United States) side by side in comparative cervical tests (CCT) using a large number of naturally infected herds in Mexico. Tuberculin from New Zealand will also be used in this comparison. All of these animals will be followed through slaughter to collect samples for culture and histopathology. From the comparisons, this study may identify a potential PPD product that could serve as a single North American reference PPD.

In addition, samples from this study could prove to be of value in the development of new diagnostic procedures.

Scientific Presentation

Regulation of Genetically-Engineered Animals and Animal Products in the United States

Richard E. Pacer
Biotechnology Regulatory Services
Veterinary Services

Genetically engineered (GE) animals hold significant promise to improve human and animal health and to benefit agriculture and the environment. Some examples of GE animals in development are disease resistant livestock, growth-rate enhanced fish, and insects engineered to reduce disease transmission.

The United States' White House Office of Science and Technology Policy is currently coordinating a process within the United States Government (USG) to clarify the authority and regulations with oversight of GE animals (including livestock, fish, and insects.) Following the Coordinated Framework outlined for the oversight of biotechnology-derived products, the two key regulatory agencies with authority over GE animals are the Food and Drug Administration (FDA), Center for Veterinary Medicine (CVM) and the United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS). The goal of the current USG discussion is to refine the multi-agency coordinated science-based system into one that is flexible, transparent, and appropriately rigorous to ensure safe development and use of GE animals with respect to human and animal health, and the environment and to instill public confidence.

USDA-APHIS has a wealth of experience in handling animal and plant health issues. Under the Plant Protection Act, APHIS has the authority and currently regulates plant pests, including GE insects, such as the pink bollworm.

Under the Animal Health Protection Act (AHPA), APHIS also has authority to protect the health of livestock. While the extent of APHIS' authority under the AHPA is still under discussion within USG, this authority can be interpreted to give USDA oversight over GE

livestock pests (such as arthropods, parasites, disease vectors, prions, and other livestock pathogens). Furthermore, this authority may extend to the GE animal itself as the transgenic animal could have altered susceptibility to a disease or pest, which might compromise its own health or the health of other livestock. In this regard, APHIS reviews requests for importation of animals and animal products from foreign countries, including those derived from genetic engineering, based on their potential to introduce exotic animal diseases and pests into the US.

Furthermore, under the authority of the Virus-Serum-Toxin Act, APHIS regulates veterinary biologicals (vaccines, bacterins, antisera, diagnostic kits, and other products of biological origin) to ensure that products available for the diagnosis, prevention, and treatment of animal diseases are pure, potent, safe, and effective. In early 2006 APHIS' Center for Veterinary Biologics approved the licensure of the first plant-based vaccine for animals. This vaccine uses tobacco cells to produce a protein that provokes an immune response in chickens to protect them against Newcastle disease.

In summary, APHIS has played and is well positioned to continue to play a significant role in the evaluation of GE animals and animal products to protect U.S. agriculture and to foster our trade of GE-derived products.

Scientific Presentation

Influence of Delivery Method on Immunologic Responses to Brucellosis Vaccines

Steven Olsen
National Animal Disease Center
Agriculture Research Center

The progress of the brucellosis (*B. abortus*) eradication program for cattle has been very successful. Dr. Olsen showed a slide depicting reduced incidence in cattle from 1982 until 1999. In 2006 only 2 states are not declared free. He stated it is possible in 2007 for all the U.S. to be brucellosis free. Dr. Olsen reviewed the development of strain RB51 vaccine starting in 1981 until 1996 when APHIS granted the conditional license to Colorado Serum. In 2003 a full license was granted to Colorado Serum.

In the Greater Yellowstone Area (GYA) brucellosis continues to be a major problem and reservoir. Alternative delivery methods for vaccination have been explored. This has involved the established ballistic delivery system using a pellet presentation. Use of a hydro gel compound has shown considerable promise. Correspondingly, vaccine development studies were launched. Evaluation was based on characterization of post-vaccination safety and immunologic responses by evaluating clearance, shedding and both humoral and cell-mediated responses. Characterization of efficacy was evaluated using a standard challenge model.

Dr. Olsen reported the comparative antibody responses of the injectable vaccine, the conventional bullet, and the hydro gel bullet. In addition to the antibody responses he reported the proliferative response and the gamma interferon response to the 3 delivery methods. The effects of delivery on the immunologic responses were summarized as follows:

1) Conventional biobullets have reduced immunologic responses

2) Reduced immunologic responses do not appear to be related to tissue damage from ballistic delivery
3) Hydro gels biobullets return immunologic to levels of hand vaccination.

Other challenges for developing brucellosis vaccines include:

1) Multiple species as targets differences in immunologic responses
2) Effective delivery of vaccine to significant portion of the targeted wildlife population
3) Need for nonliving vaccines that target protective epitopes
4) Environmental and safety issues