

REPORT OF THE COMMITTEE ON BIOLOGICS AND BIOTECHNOLOGY

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The Committee met on November 15, 2010 at the Minneapolis Hilton Hotel in Minneapolis, Minn., from 7 to 11:30 PM. There were 11 members and 25 guests present Chairman Bob Pitts welcomed everyone and reviewed the Committee's Mission Statement.

Presentations

APHIS, VS-Center for Veterinary Biologics (CVB) Update

Dr. Richard Hill, Director for the Center of Veterinary Biologics

Veterinary Services 2015 Initiative - the purpose is to make a Stronger VS for the 21st Century. As the recognized animal health leader, VS is committed to the well-being of animals, people and the environment. VS integrates One Health Principles with their business objectives along with their infrastructure to effectively collaborate with local, state, tribal, national and international partners. Dr. Hill continued by describing the organizational goals and the work groups formed to accomplish them.

The new approach for managing Bovine Tuberculosis Program was introduced. It centers upon a Concept Paper and State/Federal/Tribal Working Group that received input from five areas. The five areas are National Surveillance Strategy, the need to mitigate transmission from wildlife, the need to enhance disease response and control measures, modernizing the regulatory framework and lastly, implementation of a risk based disease management area.

The new facilities at the National Center for Animal Health (NCAH) were briefly discussed. The \$460.77 million budget has built outstanding facilities. Although Phase 1 and 2 were completed, there are still some infrastructure tasks continuing through 2011. Several demolition projects on the old animal facilities are pending.

The Program Budget for 2010 dropped back 1.5 million from the 2009 budget. Prior to 2009 the budget was much like 2010. It was pointed out that \$17.32 million was appropriated but only 12.71 million was allocated. The 2011 budget is still in the house Subcommittee and if it passes there is hope it will be much greater, greater than 17 million. The vacancy impact due to the budget is significant: 4 out of 17 Reviewer positions are unfilled; 7 out of 16 Specialists positions; 1 out of 2 Epidemiologists; 1 out of 6 Statisticians; 5 out of 18 Laboratory VMO/Micro; 7 out of 27 Technicians; 1 out of 10 Section Leaders; 6 out of 38 Support Staff; 7 out of 22 Safety and Security Unit; 5 out of 35 Information Management Unit positions.

CVB activities show an increase of 111 submissions over FY09 to 5,777, an increase of 10 new product licenses to 65, serial releases increased to 14,105, inspections decreases by 3 to 63, and the number of regulatory actions and investigations increased to 82 and 37 respectively.

The Operational Priorities in addition to the IC and PEL operations were discussed and fall into 4 areas. The first includes Single Label Claim Initiative, Electronic FOIA, and Special Labels. The second area was the Information Management System or electronic submissions. The third priority was Laboratory Development Projects related to 9 CFR regulations. Lastly, the category of In Vitro Potency Tests involving Master Reference Requalification was briefly discussed.

CVB sponsored a one day symposium on Vaccine Strategy for Swine and Swine Workers last December. Dr. Pat Foley presented information on the H1N1 Swine Influenza Virus and other Flu Viruses

Under current and emerging issues, Dr. Hill made 9 points. The first issue was about workload and staffing challenges due to the underfunded budget. The second revolved around the Cultural Transformation due to the VS2015 initiative. The third issue was the emphasis on the Operational Priorities as mentioned before. The fourth was the completion of the NCAH move and other campus activities. Fifth issue was Pharmacovigilance and it was discussed in terms of the International Guidelines and reporting via

the new Electronic Gateway approach. The sixth issue is the Refinement of the Business Plan that includes the possibility of User Fees. The seventh area was Licensing Process Program Review. The eighth issue related to upcoming meetings related to CVB priorities. These can be found on the CVB website. Lastly, it was announced that the 2011 Biologics Public Meeting was cancelled. Dr Hill explained that there is not a burning issue and the intensive time and resources to conduct this meeting can be better applied to other areas.

CVB, Policy, Evaluation and Licensing (CVB-PEL) Update

Dr. Byron Rippke, Director for the Center of Veterinary Biologics, Policy, Evaluation and Licensing

The presentation started with an organization chart showing all PEL personnel and the key vacancies. Dr. Rippke then outlined the priorities in 2010. The first area was the Mycoplasma PCR test development, followed by Extraneous Agent Microarray development, Licensing-Serial-Release- Testing-Information-System (LSRTS) implementation, BID Section testing backlog, and firm merger activities. Application Review was the second priority as applied to new and existing products. Thirdly, as part of the Veterinary Service 2015 Initiative, PEL will give emphasis to management and culture review activities. Fourth area was the area of Program Documentation and Quality Assurance that resulted in 10 new published Notices, 2 new Memos, 11 posted documents on the CVB Website for comment, and one Federal Register Notice publication. The last priority was swine Flu, H1N1.

There are 77 Establishment Licenses and 22 Permittee currently regulated by CVB. From those establishments there are 1,942 active product licenses. Fifty seven of those were issued thus far in FY 2010. Over the past ten years there has been a gradual decrease in the number of establishments and product licenses. This is primarily due to company mergers. There were 18,721 serial submitted and 728 were pulled for testing (4.31%) Of those, 8 were found unsatisfactory. Lastly, CVB shipped 3,939 vials of reagents of which 33 went to foreign locations.

CVB, Inspection and Compliance (CVB-IC) Update

Presented by Dr. Byron Rippke in the absence of Steve Karli, the Director of CVB, Inspection and Compliance

Licensing, Serial Release, Testing Information System (LSRTIS) implementation was a major endeavor in 2010. This new system provides the serial release processing, tracking, and authorization for over 73 billion doses of vaccine and related animal biologic products. It provides the flow processing for licensing and prelicensing of over 124 manufacturers and more than 2,500 products. The certification and accreditation, Phase II was recently initiated.

Pharmacovigilance is intended to improve adverse event reporting and track the safety of licensed products. This also provides CVB with a system that meets international regulatory requirements for pharmacovigilance. This initiative uses off the shelf software and is the process of certification and accreditation. Plans in 2011 are to interface with the FDA and EPA.

The remaining time of this presentation showed the inspection activity for 2010 compared to years past. For specific information, the slides are available on the CVB website.

Panel Discussion: Industry Perspectives on CVB Budget Challenges

- Dr. Richard Hill, Director for the Center of Veterinary Biologics
- Bob Tully, Livestock Products Manager, Biomune/Ceva
- Joe O'Donnell, Regulatory Affairs Manager, IDEXX
- Joe Huff, President, Colorado Serum Company

Each participant gave initial evaluations on the effect of CVB's funding problems over the past years. Essentially, CVB has been flat funded for many years and is unable to fill many vacancies as described in Dr. Hill's presentation preceding this discussion. Each of the industry representatives indicated increased times for approvals, reviews and testing and believed it was due to resource constraints. One company also saw quality issues and personnel issues. It was also brought up that new initiatives, unrelated to the core activities, were interfering with current workloads. "If you find yourself in a hole, you should stop digging." All these delays come at a time when biological science is faced with greater responsibilities relative to food

safety and biosecurity issues. Another panel member expressed their company's concern about the commitment to new product and locations to manufacture them - the world has shrunk and other country's markets and regulatory climates can dictate a company's redirected resources. Dr. Hill pointed out the strong relationship CVB has with the industry and has solicited input in the past. Several trade organizations have submitted letters with their priorities and CVB listened. It was pointed out this committee has passed resolutions in the past asking Congress to increase CVB funding without success.

The topic of International Harmonization and particularly CVB's involvement with VICH activities was discussed. There is concern this time consuming commitment takes up too much resources and little has been accomplished. One industry representative described it as a "rocky road" and was not optimistic about further significant progress. Although the possible outcome would make registration in foreign countries easier, the feeling was CVB could better use their limited resources in more meaningful ways.

All three company representatives were against the use of user fees. There was concern that it could potentially limit the number of products that are now available and prevent the applications of products with smaller markets. It was expressed that the approximately five million dollars CVB would gain in User Fees was better appropriated directly from congress because it has the responsibility to publicly fund animal health, safety and welfare matters. Another comment was the FDA model was not a good template for the veterinary biological industry.

One comment expressed from the audience showed frustration with congress for continually cutting back on the President's Budget. It was pointed out by one industry representative, that the approximately seventeen million dollar CVB budget was a real bargain and a great investment by the USDA when considering the impact veterinary biological and diagnostic has on the multi-billion dollar allied industries that require these products to further their businesses. Dr Hill commented that User Fees has been part of the President's Budget for 3 years, but not in the Congressional Allocation.

Unfortunately, time ran out on this timely, lively and important discussion. It should be noted that CVB generally does an outstanding job considering the workload and time constraints. The criticisms expressed during this panel were intended to be helpful to CVB.

Roadmap for Creating the New NADC: 2010 – 2015

Dr. Kurt Zulke, Director for the National Animal Disease Center (NADC), U.S. Department of Agriculture (USDA)

Dr. Zulke divided his presentation into 3 parts:

1) Update on USDA Ames Modernization Project: Major construction is completed on all new facilities and all but a few select agent labs are now operating out of the new space. Current emphasis is on decommissioning and demolishing older buildings to complete the modernization project and decrease overall operating costs.

2) Creating of the USDA National Centers for Animal Health (NCAH): The NCAH is an interagency partnership between USDA APHIS and ARS and is comprised of the new shared facilities and 6 newly created combined support services units that provide operational support to the NADC, NVSL, and CVB. A major interagency milestone was achieved with the completion of the final NCAH combined service unit (the Administrative support unit) in September 2010. The NCAH combined services units comprise a \$28M joint support business and are managed by an interagency Board of Directors comprised of Director and Deputy Director of NADC, and Directors of APHIS CVB and NVSL.

3) Business Planning to Create the New NADC: The newly constructed USDA NCAH facilities are among the most extensive and advanced high-containment large animal disease research facilities in the world; there are probably fewer than five comparable facilities world-wide. These state of the art facilities combined with concurrent advances in the scientific fields of genomics, microbial ecology, immunology, and systems biology are converging to create an unprecedented opportunity for NADC scientists to build upon their strong tradition of leadership in animal health research to create a new center that can once again define innovation and global leadership animal health and food safety research. NADC business plans were developed at the Center and individual Management Unit level during FY10. A core to this planning process was the need to focus and reposition NADC's scientific and research expertise to maximize impact to best address our National priorities while positioning the Center for future growth. NADC's strategic science themes for 2010 – 2015 are: Cattle diseases associated with immune dysfunction; Zoonotic diseases in livestock and wildlife species; Emerging diseases (currently emphasizing viral diseases in swine (e.g. swine influenza virus)); and, Microbial ecology in food safety

and animal health. A major emphasis in all NADC research is adaptation and application of biotechnology, genomics, proteomics and bioinformatics towards solving the most important animal health and food safety problems of today and tomorrow. Lastly, Dr. Zuelke provided the Committee with an overview sample of some of the most current research activities and highlights within each of the Center's strategic science themes.

Dr. James Wolfram

Consultant for Civilian Research and Development Foundation (CRDF)

Dr. Jim Wolfram introduced the last three Russian presenters. Dr. Wolfram has worked with these scientists for over a decade via the Non Proliferation programs that the US Government sponsors. Both countries are having some reoccurrence of brucellosis in bovine species. A joint project was funded to share data and to perform some comparative laboratory studies on the vaccines that both countries are now using to control this zoonotic disease. Yellowstone Park scientists led the initial meeting outlining the wild animal brucellosis infection. Then in 2005, this delegation attended the Laramie WY conference and presented data on Strain 82 vaccine, a live *Brucella abortus* strain. The Road Map that was developed from that meeting as a guide stated that before the US sponsors the development of a new vaccine, other vaccines should be tested to determine if they would be efficacious in wild animals. The request was made that the Russian data on Strain 82, the vaccine that has been utilized in their cattle herds since 1975, which replaced Strain 19 vaccine in 1974 be published in the western open literature. In 2008, the United States sponsored a Transboundary Zoonotic Disease-Brucellosis Workshop in Serpukhov Russia. In 2010, the Journal, Vaccine, published the presentations from that workshop as a special issue, Vol. 28, supplement 5, 1 Oct. 2010 and another article now in press with the Journal of Animal Health Reviews, are manuscripts that describe the data on Russian vaccines for the prevention of brucellosis. To continue what the Laramie workshop started the delegation returned to further discuss their efforts on brucellosis at this 114th USAHA meeting in Minneapolis.

Research on Animal Biologics in Russia

Dr. Aleksander Denisov, Head of Molecular Genetics & Immunology Department, State Federal Enterprise for Science, Research Center for Toxicology and Hygienic Regulation of Biopreparations, Serpukhov, Russia

The main research conducted by Russian scientists in the field of animal biologics as well as the results of adjuvant application for immunopotentiating of live brucellosis vaccines are presented.

The main research lines are:

- Development of different kinds of vaccines, which cover a wide spectrum of bacterial and viral infections.
- Development of probiotic preparations as alternatives to antibiotics (isolation of probiotic bacteria from natural resources, isolation and purification of biologically active compounds from them, such as bacteriocines, investigation of their properties, genetic constructing of new recombinant probiotics and so on).
- Development/application of immunopotentiators/adjuvants for modern vaccines.

Because vaccination remains the single most effective method for preventing infectious diseases, development of novel vaccines takes a larger part of the research. Vaccination efficiency depends directly on efficiency of the vaccine, host-specificity, exogenous factors and the route of vaccine administration. If we want to provide effective protection against infections, the route of vaccine administration must imitate the natural route of infectious agent penetration.

In addition to development a novel more efficacious vaccines, one possible mechanism to improve efficacy of currently available vaccines is to use immunopotentiating compounds, such as adjuvants, together with these vaccines.

Today there is no ideal brucellosis vaccine that provides protection against all species of brucella in all species of animals. That's why we tried to study the availability of different adjuvants to enhance and modulate antigen-specific immunoresponses after their administration with live brucellosis vaccine. As the criteria for evaluation of adjuvants' efficacy, we study their influence on humoral, cellular immunity, phagocytosis by macrophages and protection against experimental challenging with virulent *B. abortus* strain. Our studies demonstrated that adjuvants can be successfully used for stimulation of humoral and cellular immune responses to live brucellosis vaccine. Selection of specific adjuvant depends on the type of

immunity to be induced and on host specific immune response. To provide effective protection, the adjuvants stimulating primarily a weak link of immunity in the target animal should be used.

Dr. Konstantin Salmakov

Doctor of Veterinary Sciences, Head of Department of Brucellosis, All Russian Veterinary Institute, Kazan, Russia

Experience of 50-years control of cattle brucellosis in the Russian Federation and CIS countries as well as the history of development, characteristic, immunological efficiency, results of numerous testing and trials of *B. abortus* 82 vaccine against brucellosis in animal models are presented.

A vaccine from strain *B. abortus* 82 was widely applied for immunization of cattle in many republics of the former USSR (Russia, Azerbaijan, Georgia, Armenia, Tadjikistan, Kirghizia, Turkmanistan, Kazakhstan, etc.).

Creation of enough strong immune background due to wide application of a vaccine from strain *B. abortus* 82 and an opportunity of early post-vaccinal diagnostics has allowed in short time to eradicate brucellosis in many cattle-breeding facilities of Russian Federations and some of the CIS countries. By 2008 in Russia, the number of brucellosis infected points and cases of cattle brucellosis were reduced more than 75 times. Many regions have free-brucellosis status, including Ural and Siberian Federal district, where the difficult situation with brucellosis was noted for the past several years.

Positive results on improvement of situation with cattle brucellosis after strain *B. abortus* 82 applications have been obtained in a number of the CIS countries as well. In Transcaucasia Republics (Azerbaijan, Georgia, Armenia) and Central Asia (Tadjikistan, etc.) within 1974-1984 years significant reduction of brucellosis infected points and cases of cattle brucellosis was noted.

According to Russian scientists' data, positive results of vaccine 82 applications have been received on other kinds of animals (bison, sheep, pigs, reindeers, soils, yaks, buffaloes, zebu, and camels).

In 1988 after establishment of high anti-epizootic efficiency the live vaccine from strain *B. abortus* 82 has been accepted in veterinary practice for control of cattle brucellosis. One of the last studies of *B. abortus* 82 vaccine was conducted within the framework of the ISTC Project #2434 "(2003-2007). The main goal of these studies were comparative studying of immunobiological properties of Russian and American *B. abortus* vaccine strains and selection of the most effective vaccine for specific prophylaxis of bison's brucellosis in Yellowstone National Park (YNP).

Our data obtained and a large experience in control of brucellosis in Russia let us assert that application of *B. abortus* 82 vaccine under developed schemes for each level of epizootic intensity allows achieving appreciable results on prevention and eradication of cattle brucellosis in the general complex of veterinary-sanitary actions.

B. abortus 82 vaccine can be recommended for eradication of brucellosis in wildlife. Additional trials of *B. abortus* 82 vaccine on bison or elk models are required prior to its application in YNP.

Russian State System for Registering and Certification of Veterinary Biologicals and Drugs

Dr. Oleg Skliarov, Head of Department, All-Russian State Research Institute for Control, Standardization and Certification of Veterinary Preparations, Moscow, Russia

Dr. Oleg Sklyarov, Head of the division for Quality and Standardization of Immunobiological Medical Products for Animals, at the All-Russian State Center for Quality and Standardization of Medical Products for Animals and Forages in the Ministry of Agriculture for the Russian Federation in Moscow, Russia. Oleg has his Ph.D. and Dr. of Science in veterinary Medicine and has worked as a veterinarian.

His presentation focused on the procedural process that is used in Russian to register and certify animal medical products. He indicated that the Russian Federation (RF) is experiencing an increase in volume of veterinary products requiring registration. During the last three years, 2007-09, there have been a total of 2300 plus products registered. About half of these registrations have come from foreign countries.

The RF requires by law that a specific set of criteria have to be followed not only to register a product but also for its certification and licensing for production. In a diagram, Dr. Sklyarov presented the steps in the registration process, some of which have recently, April 2010, been changed to streamline the process. One of the steps requires and independent outside examination of the product. All stages of the process are now open and published on the Internet.

Certification process includes laboratory analyses of all ingredients stated in the product, an evaluation of the QC assurance for the production of the product, and an examination of the manufacturing facility which makes the product. Another diagram was provided detailing the steps for certification. The RF routinely certifies over 1000 biological animal products per annum. This certification program also declines products that are non-effective, dangerous, or of poor quality. From 1998 to 2008, 732 poor quality medical products including 178 biological preparations were discontinued or eliminated.

Medical products for animals require the manufacturing facility be licensed. The manufacturer's licensing is standardized by the RF. Russian standards now use international ISO 9000 criteria incorporating the rules of GMP, GLP, and GCP.

Committee Business

The members were asked to review and comment on the latest OIE listed Chapters at http://www.aphis.usda.gov/import_export/animals/oie/terrestrial.shtml . USAHA would like our comments before December 1. Individuals can also comment directly.

A Resolution was proposed by Dr. Randal Berrier, Colorado Serum, to update 9CFR 113.450. This regulation requires several diagnostic tests on serum producing animals used as antibody production that are not applicable due to disease free status in the US. This revision would save firms time, expense but more importantly the problems faced with false positives that in the case of TB has lead to unnecessary deaths to prove disease free status. The resolution was passed unanimously and will be submitted to the Committee on Nominations and Resolutions.