REPORT OF THE COMMITTEE ON BIOLOGICS AND BIOTECHNOLOGY

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The Committee met on October 21st, 2014 at the Sheraton Hotel in Kansas City, Missouri, from 1:00 – 5:30. There were 12 members and 19 guests present. The meeting was called to order at 1:00 PM. There were no previous resolutions or other business to discuss.

Presentations & Reports

Proposal for Rational Swine Influenza Vaccine Design

Dr. Amy Vincent, USDA/ARS/National Animal Disease Center

An integrated multi-agency approach is needed for improving influenza virus vaccine strain selection for use in swine, ideally with representatives from ARS, APHIS, NAHLN labs, and Industry. The USDA SIV Surveillance System must continue to monitor contemporary viruses identified in cases of respiratory disease outbreak investigations through veterinary/producer participation and submissions to NAHLN labs. Trends in changing subtypes or genetic evolution should be monitored by sequence analysis specialists. Representative viruses from predominant subtypes or genotypes should be evaluated at an antigenic level by serologic cross-reactivity with vaccine anti-sera. New anti-sera should be generated with antigenic drift viruses or with newly added vaccine strains. *In vivo* swine studies should be conducted when viruses with substantial changes have been identified or when vaccine strains have been substantially changed.

One or more influenza A virus backbones should be approved by CVB for ease of quickly generating viruses with new and relevant hemagglutinins (HA) and neuraminidases (NA) for vaccine purposes. Backbones should be demonstrated to provide attenuation in the case of MLV as well as exhibiting high yield growth properties as a vaccine seed for influenza A virus vaccines for use in swine. The advantage to this is:

- Not all field strains provide sufficient antigenic mass of HA and this would facilitate the ease of testing several representative strains to select the optimal isolate.
- Not all field strains grow well in culture and this would facilitate the ease of testing several representative strains to select the optimal isolate.
- Reduces the risk of introducing extraneous agents from field isolates.

By way of traditional reassortment or reverse genetics, licensed manufacturers generate reassortant viruses with relevant HA and NA found to circulate in pigs or that pose a significant risk to pigs (like the 2009 pandemic virus first found in humans) in order to meet the industry's needs. A company should be required to notify CVB of the HA and/or NA sequences being incorporated onto the approved backbone, adhere to previously approved Good Manufacturing Process practices, and get vaccine updates on the market without delay. Minimal safety and efficacy data should be required if the previously approved seed strain backbone and vaccine formulation is used, but should minimally demonstrate strong serologic cross-reactivity with homologous and heterologous contemporary strains. Companies may select HA and NA sequences from the USDA SIV surveillance system or from their own internal surveillance data for their customers. Viruses from the USDA SIV Surveillance Repository are available for this purpose.

Advantages of this over our current system:

- Vaccines can be rapidly engineered and manufactured to meet industry needs with less R&D investment from companies.
- Killed vaccines may still be made available but would be much improved by more rapid and cost effective regular updates of vaccine strains.
- Inactivated vaccine efficacy is reduced by maternal antibody and inactivated vaccines can have adverse effects in certain cases of virus strain mismatches. MLV/attenuated or vectored vaccines maintain greater efficacy in the face of maternal antibody compared to inactivated vaccines.

- MLV/attenuated or vectored vaccines have been proven superior to killed for protection against heterologous strains.
- More doses of an MLV/attenuated or vectored vaccine may be mass-produced in the event of an emergency due to the reduced amount of virus required in the vaccine.

Role of Autogenous Products in Emerging Diseases Outbreaks and for Diseases with High Antigenic Diversity

Dr. Doug Stine, Newport Laboratories

Dr. Stine discussed the use of autogenous products, and discussed the 9CFR 113.113 requirements for autogenous products. He went on to describe the successful use of autogenous products for control of swine influenza. After pandemic flu introduction, they found that they had strains in their collection that protected against the H5N1 pandemic strain. They continue to raise additional swine reference antisera and add it to their panel to monitor neutralizing activity. There is continued spillover of human flu into swine populations. This requires continuous monitoring of nonreactive strains. Success is dependent on accessible cell lines for viral growth.

An example of a "failure" with autogenous products is the 2013-2014 rotavirus occurrence. ISU submissions year to date are 3,618 positive samples. Newport only has a 25% success rate for rotavirus group A, and 0% for group C. This is due to lack of cell lines susceptible to the viruses. There is significant genetic diversity among isolates. The current method of control for rotavirus is back feeding piglets to susceptible sows. This is archaic and antiquated, and raises disease spread and animal welfare concerns.

PEDv is the latest emerging disease they're trying to deal with, complicated with circulation of swine delta coronavirus. There are two conditional products in the U.S. Globally there are multiple MLV and killed vaccines. The current industry response is feed back of live virus (serum or intestinal contents) to sows. Feed backs contain rotavirus, but possibly other pathogens, and is potentially a dangerous practice. Further, this forces producers to look to use of 9 CFR 107.1.

What could the alternative be? Vectored autogenous subunit vaccines should be an option. Make use of advances in molecular biology to produce viral subunit vaccines. This would avoid potential transfer of adventitious agents. A vector platform for autogenous products should be considered.

Center for Veterinary Biologics Updates

Dr. Byron Rippke, USDA/APHIS/VS/STAS/Center for Veterinary Biologics

Dr. Rippke provided updates on the following topics:

CVD Director Search/Staffing: The announcements have closed, and the hiring certificates have been issued. The process has been taking a year to 14 months. The position should be filled within the next couple of months.

Budget: 2014 budget is $16,417,00. This is a slight increase over 2013. There is some funding to hire, but it's taking a long time to fill positions.

Business Process Improvement Projects (BPI): a major project has been to build ability for receiving electronic licensing submissions. They're currently looking to expand this to Outlines of Production and labels. Also, they're working on electronic licensing plans and #1 files, and developing the infrastructure for an electronic portal. There is some work being done to develop a process for electronic serial release. APHIS is trying to integrate electronic processes, and how CVB fits into those efforts remains to be seen. Future projects include Master Seed/Master Cell testing processes.

Inspection and Compliance (IC) update: LSRTIS is the primary information management system. It touches virtually every part of the CVB's operations. A big effort around LSRTIS in 2014 has been Certification and Accreditation of the system. The current system has the authority to operate until July 2017. The system was moved to the National Information Technology Center in Kansas City in 2014.

Electronic Notification of Serial Release was fully implemented in 2013. Enhancements were implemented in August 2014.

Pharmacovigilance via PV Works was implemented. This provides CVB with a system that meets VICH harmonized guidelines. This enables CVB to receive and process greater numbers of adverse event reports (AERs). CVB is finalizing a new proposed rule that will require mandatory periodic submission of AER data from Market Authorization Holders. Public comments have been addressed. The rule is currently under review by the APHIS Regulatory Analysis and Development staff. IC focus is on decreasing regulatory burden while maintaining integrity of the regulatory system.

IC is looking for non-regulatory solutions, enhanced transparency, and quality of manufacturing.

PEL update:

Draft Memorandum 440: release specifications ("antigen overage"). This looks at a more data-driven approach to establishing release specifications. There will be a 2-day stakeholder workshop to discuss the issues. This will result in another draft Memorandum for industry comment.

9CFR 107.1, Veterinary Exemption. The rule doesn't allow for 3rd party manufacture. The final rule is currently under Office of General Counsel review. Expect to see this within the next few months. Along with this are draft Memos 800.213 and 800.111. This guidance would help allow companies to get products out quickly without resorting to 107.1.

Single tier label claims: One of the first BPI efforts, it's geared toward how information is presented to the user and provides more meaningful information to the user to better assess product performance. Two components: 1) label would state, "this product has been shown to be effective for the vaccination of/against…". 2) Second component would be data summaries of efficacy/safety data used to license the product, which would be available on the CB website for public viewing. It will include a user guide. Implementation will be done by species group, and will be staged over the next 4-6 years. They anticipate that it will be published in the first couple of months of 2015.

Needs and Risks Related to Use of Fetal Bovine Serum (FBS) in Veterinary Biologics (panel presentations):

Topic Introduction

Dr. Julia Ridpath, USDA/ARS/National Animal Disease Center

An oft repeated rumor is that New Zealand is exporting far more FBS than could possibly be produced in that country. BVDV costs the cattle industry at least $400 Million/year. There are numerous examples of contaminated FBS used in vaccines or other products. CSF has been detected in lots of FBS found in China. A number of viruses have emerged since the 9CFR regulations were written. Complicating the issue is that you can only test for what you know. We have more sensitive tests now, and very different pathogens than what were available when the regulations were written.

Importation Requirements for FBS

Dr. Tracye Butler, USDA/APHIA/VS/National Import-Export Services

USDA takes a very conservative approach because of wide dissemination. Currently, importation is allowed from Canada, Mexico, Central America, New Zealand, Australia, and Chile. This requires country certification that the animals were born in that country. Samples are collected from commercial imports that originated in all eligible countries except Canada and New Zealand. There are no NIES requirements for labeling. Samples remain in quarantine until completion of safety testing. One liter of the lot can be imported for the client specification testing. If there are positive results, the material can be re-exported at owner's expense or destroyed at owner's expense. There is a Risk Assessment underway with a delivery date not later than August 31, 2015.

A BSE comprehensive rule was finalized in 2013, effective March 2014. It established BSE-related import provisions to align with OIE guidelines. Now there are more markets from which to import bovine serum. NIES is updating the import requirements for FBS from each BSE risk category. The scope of the new risk assessment is for FBS, newborn calf, donor bovine serum, BSA, and some other blood products.

CVB Testing Requirements for FBS used in Veterinary Biologics

Dr. Geetha Srinivas, USDA/APHIS/VS/STAS/Center for Veterinary Biologics

Dr. Byron Rippke gave the presentation. Testing requirements for FBS include 9CFR 113.53, which refers to other regulations as well. Ingredients of animal origin must come from countries defined as no risk or low risk for BSE as defined by the NCIE (now NIES) and 9CFR 94.18. Factors outside of CVB regulatory authority include relabeling of imported FBS, and blending of US material with imported FBS Industry concerns include cost and availability, contamination, country of origin labeling, possibility of counterfeit FBS.

Biologics Industry Best Practices for Using FBS in Veterinary Biologics

Dr. Kent McClure, General Counsel, Animal Health Institute

AHI is an industry group that represents over 95% of the US biologics manufacturers. FBS is an essential ingredient of cell culture media used in production of many biologicals. Quality of the serum can have dramatic impacts on the quality of biologics. Alternatives are routinely investigated during

development. The business approach is very cautious. The regulatory responsibility lies with the manufacturer. They limit the country of origin to US, Canada Australia/NZ. They test to the highest possible level, and in fact to a higher level than is required by any government. Material is tested for mycoplasma, bacteria, fungi, and extraneous viruses. Further screening is also conducted to confirm purity and identity, including electrophoresis, osmolarity, total protein, hemoglobin, physiochemical testing, and other assays. Also, testing is done for cytopathic and hemadsorbing agents, FA tests for specific agents, and agents of major concerns for or regional importance. Testing is relevant to the product and to the manufacturer. When emerging diseases are identified, those are added to the testing repertoire. Samples are tested before and after validated irradiation. Finally, animal screening is conducted prior to use of the FBS in manufacturing.

Standards tested to: USDA, FDA, EMEA, Australian, EU Pharmacopoeia, USA, GLP, GMP, ISO 9001. Validated irradiation is done at 25-50 kGy; the EU standard is 30kGy. Testing is done on pre-and post-irradiated samples. Typical irradiation reduction for BVDV is 10^6.

Validation of virus inactivation includes multiple steps, and the impacts of many factors are considered. Vendor audits are standard practice as part of the companies' quality management system. Things that are looked at include acquisition/disposition records, traceability systems, and quality assurance systems. These audits are more stringent than government inspection. The International Serum Industry Association offers an extensive process for certification. All records are available for audit, from harvest to testing to sales.

Proposed Importation of Irradiated FBS from FMD Free Countries (Free with Vaccination)
Dr. Percy Hawkes, Consultant for Biowest USA

Dr. Hawkes presented the following position in his presentation: the FBS industry recognizes that APHIS has the responsibility of ensuring that fetal bovine serum (FBS) imported from other countries is free of pathogens which do not exist in the United States and pose a risk to the U.S. livestock population. Yet, the limited supply of USDA approved FBS has not been able to keep up with the demand, and this has resulted in price differences that make USDA approved FBS as much as 12 times higher than non-USDA approved FBS. This price difference rewards smuggling and misrepresentation of FBS between origins, thus putting at risk the traceability and safety of "USDA approved FBS", throughout the world. Gamma irradiation has been used by USDA-APHIS-VS for several decades as a method to inactivate potential pathogens in ruminant serum imported from countries known to have livestock diseases that do not occur in the United States. Importations of ruminant serum have been authorized by USDA-APHIS-VS in limited quantities for developmental research and diagnostic purposes by both governmental and private institutions. Gamma irradiation is also routinely used by the serum industry to ensure compliance with 9CFR 113.28, 46, 47, and 53, to inactivate adventitious pathogens of concern. In addition, gamma irradiation is routinely used to eliminate potential pathogens in medical products used for both human and animal medical applications. Gamma irradiation is also routinely used by USDA for the treatment of many food products of animal and plant origin. Ten years ago, Resolution Number 13, approved at the 2004 United States Animal Health Association (USAHA) annual meeting, recommended that USDA-APHIS allow the importation of gamma irradiated commercial shipments of FBS. USDA-APHIS responded by completing a risk assessment and preparing a proposed rule, which was promised to be published in 2008. However, due to other pressing priorities APHIS has not yet published this proposed rule. In 2014, APHIS has announced that they have requested an in depth risk assessment for imported bovine sera, including Fetal Bovine Serum, in preparation for updating import requirements. In light of this announcement, the FBS industry requests that the Biologics and Biotechnology Committee recommend that APHIS follow up and publish the proposed rule prepared and promised by APHIS in 2008 to allow the importation of gamma irradiated FBS from FMD free countries with vaccination. The FBS industry also recommends that the Biologics and Biotechnology Committee urge USDA, APHIS, VS to work with the FBS industry to include the following options when updating FBS import requirements: 1) Irradiation outside the US with proper USDA oversight, 2) Importation of irradiated FBS from FMD free countries with vaccination, 3) Processing of FBS in 3rd countries with proper USDA oversight, 4) Safety testing of FBS using internationally accepted tests other than animal inoculation, and 5) Define penalties for fraud and misrepresentation.

Committee Business:

A resolution was presented by Percy Hawkes, entitled, "Importation of Fetal Bovine Serum". His resolution was passed earlier this week by the Committee on Import-Export. The motion to "accept as written" failed for lack of a second.

A resolution was presented by Chuck Massengill, Vice-Chair of the Committee on Infection Diseases of Cattle, Bison, and Camelids, entitled “Importation of Fetal Bovine Serum”. A motion was made for a new and revised resolution from the Committee for Biologics and Biotechnology entitled, “Standards for Fetal Bovine Serum”. The motion was seconded and passed on a vote of 9 to zero.

A resolution was presented by Joe Huff entitled, “Manufacturing of Veterinary Biologicals Without Licensure”. A motion was made to accept as written. The motion was seconded and passed on a vote of 9 to zero.

Being no further business, the meeting adjourned at 5:00 PM.