REPORT OF THE COMMITTEE ON BIOLOGICS AND BIOTECHNOLOGY

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The Committee met on October 18, 2016 at the Sheraton Greensboro Hotel in Greensboro, North Carolina from 1:00 to 4:00 p.m. There were 12 members and 12 guests present. The meeting was called to order, introductions were made, and previous resolutions were reviewed. The committee agreed that the interim responses to the previous resolutions were satisfactory.

Presentations and Reports

Updates on Activities with the International Serum Industry Association

Rosemary Versteegen, International Serum Industry Association (ISIA)

Dr. Versteegen introduced the association and its mission. The ISIA focuses on the ethics of the industry. They have worked toward standardization of the definition of “serum”, standardization of testing processes, and are engaging in efforts to confirm source traceability, and tests to identify country of origin. ISIA worked with U.S. Pharmacopoeia (USP) to establish standardized testing protocol for serum products. They also have a gamma irradiation task force to develop guidance and informational documents related to gamma irradiation processes appropriate for serum products.

Membership in ISIA requires audits to confirm that traceability processes are established and practiced. Independent audits are conducted to cover all transactions in the company. Audits focus on each handoff of material. For example, it came in at what price? Went out at what price? Not just origin, but also paperwork for exportation, what kind of serum it is, blending of serum types etc. Companies have to be certified to be a member and undergo the auditing process. Seventy percent (70%) of serum companies two years or older are certified, and more than 90% of all animal serum used globally is provided by ISIA certified members.

Geographic origin: tests for strontium isotopes were evaluated but it was learned that this approach can’t distinguish serum from Mexico versus serum from the U.S. Another approach is the use of trace elements. Very clear groupings emerge from this approach. Ninety nine percent (99%) resolution was achieved with their current data set. As a result, the group is working to define an industry database and develop a program to identify geographic origin. In addition, they are monitoring other technologies to determine geographic origin, animal age, and species of serum products.

Looking to the future: a combination of testing and paperwork audit will strengthen the program. Increased focus from customers and regulators will also strengthen the program.

Gamma Irradiation Task Force: last year, a resolution was made at the USAHA meeting to allow fetal bovine serum (FBS) irradiated outside the USA to be imported. The resolution did not pass, and the USDA and USAHA know there is a need to understand the subject better. ISIA is working on a project to clarify gamma irradiation and its role in helping to ensure that serum is free from extraneous agents.

Participants in the task force include suppliers, vendors, and end users. Everyone agreed that they would not wait until this is perfect to begin publishing. Segments/parts of the work are published as ready. Food and Drug Administration (FDA) requested that the information be freely available, so all articles are being published in BioProcesing Journal as open access: www.**bioprocessingjournal**.com

Status of the various parts:

- Introduction to gamma irradiation and serum: Published
- Effect of gamma irradiation on viruses: Published
- Dose mapping and validation: In final editing
- Effect of gamma irradiation on polymers: Almost final

- Product maintenance through the process: Outline complete
- What does this all mean? Waiting for solid drafts of first 5

The presentation can be found on the Committee page at www.usaha.org.

Center for Veterinary Biologics Updates

Byron Rippke, USDA-APHIS-VS-STAS, Center for Veterinary Biologics (CVB)

- End of year numbers regarding #licenses, doses released, etc. will be posted on the CVB website: https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics
- Staffing & budget: FY 2015-16 has been a flat budget. Further, a flat budget expected through 2018. Funding has been static over the past ten years, so there has been a net loss in funding. The majority of funding goes to salaries so they have lost about a third of their staff. Consequently, they're constantly looking for ways to do things more efficiently.
- New labeling: this simplifies efficacy claims
- National Centers for Animal Health (NCAH) portal: access is based on Level 2 USDA e-authorization credentials. The system is entirely paperless. Customer entry is based on familiar APHIS forms. Supporting documents can be uploaded, and the system interacts directly with the CVB database. Efficiencies: time and costs associated with printing and mailing submissions and regulatory responses. It securely maintains a complete list of pending submissions for each establishment, with current review status. It allows simultaneous access to the same information for every authorized user at an establishment. This facilitates team assembly of submissions.
- Categorical exclusion status: proposed rule comment period closed, and comments have been responded to. Publication of final rule is not known.
- National Import Export Services (NIES) Serum Risk Assessment (RA) status: set back a year due to highly pathogenic avian influenza (HPAI). An initial draft was commented on by the RA customers. It is still being worked on but not finished. Timeline is unknown.
- Veterinary International Conference on Harmonization (VICH) Extraneous Agent Testing Working Group: the group is reactivated but details about status are unavailable.
- Pharmacovigilance proposed rule published fall of 2015. All comments have been addressed and signed off through department. The final rule should be published, but date is unknown.

U.S. Industry Considerations When Pursuing Licensure of Wildlife Vaccines

Mark Wood, Merial

The purpose of this presentation is to present the realities of the issues associated with licensing wildlife vaccines.

There are three main regulatory authorities:

1. USDA under 9 CFR: this covers immune-based products to prevent, treat, or diagnose animal diseases
2. Food and Drug Administration (FDA) under 21 CFR: contraceptives, performance-based vaccines, and all others not covered by the USDA
3. Environmental Protection Agency (EPA) under 40 CFR: insecticides, fungicides, rodenticides. Includes contraceptives to manage wildlife populations, such as Gonacon

Wildlife vaccines are niche products:

- Not high volume
- Most of their use provisions are restricted to government licensed programs
- Products must be produced at minimal cost

Within 9 CFR, there are basically three streamlined pathways that might be applied to the use of these products:

1. Part 102.6—Conditional licensure. Must be pure and safe and in compliance with all applicable regulations and standard, and may be restricted. Branding is not allowed, and approval from State Veterinarians is required. Conditional licenses require renewal based on the approved term, and renewal is not assured.
2. Part 103.3—experimental use. This may be a temporary pathway, but there are concerns about continuity. There is no commercial branding, labeling, or competitive support provided for this

approach. Perpetual 103.3 authorizations have been utilized but there are concerns about how long those will be allowed to continue.

3. Part 106—exemption for products used in department programs or under department control or supervision. This provision is rarely used and has not previously been applied to wildlife vaccines.

Timelines to full licensure:

- Conventional products: 3-4+ years
- Live biotech products: 4-5+ years

Evaluation of wildlife product efficacy should consider field-based analyses including epidemiological approaches and population immunity models. Disease surveillance systems in the field should be considered, as well as immunity sufficient to break field transmission/disease cycles.

Investment incentives are needed for the following reasons:

- Sales volumes are often low, but the cost of goods is typically higher
- Production needs are sporadic (unpredictable forecasts), making production planning problematic
- Low state federal program budgets = minimal return on investment (ROI), thus profit margins are typically lower than commercial products.

Other difficulties encountered include:

- Regulatory oversight is not always clear (USDA-FDA, Environmental Protection Agency (EPA))
- Products are largely orphan, neglected—there are limited/no specified regulations or commercial incentives for investors/sponsors
- Regulatory hurdles—field data have little/no review/acceptance provisions to support pivotal efficacy study consideration
- It is sometimes difficult to justify research and development (R&D) costs for vaccines that compete for the same development resources needed for conventional vaccines.

Possible areas for future consideration to help support wildlife vaccines:

1. Consider coordinated review team approach for a more specialized evaluation of these products
2. Consider regulatory memos/guidelines specific to the licensure of wildlife vaccines
3. Allow global U.S. companies the opportunity to build on the development work done in other countries—consider the use of those data generated internationally (if applicable) to support product safety, reasonable expectation of efficacy, and/or other product attributes
4. Consider conditional claims to expand the use provisions for currently licensed products, e.g., additional species claims
5. Make provisions for assembly/submission/review/approval of field efficacy data

Animal Health Institute

Kent McClure, Animal Health Institute

Biological issues at Animal Health Institute (AHI):

Dr. McClure covered a lot of issues of interest to AHI that don't need to be repeated. In the industry, there have been some unprecedented changes taking place with regards to regulatory issues. The National Centers for Animal Health (NCAH) portal is a major accomplishment that the industry applauds and embraces. Changes in labeling requirements were not necessarily welcome, but we recognize they were a customer-driven initiative. Veterinarians wanted different information about the products they're using, and the Center for Veterinary Biologics (CVB) has done their best to satisfy customer needs while at the same time accommodating the needs of the regulated industry. Categorical exclusions were a monumental advance that will eventually allow industry to move quickly to address emerging/evolving disease problems.

Another big topic is related to the potency assay for conventional inactivated rabies products. The current potency test for rabies is a mouse challenge assay. This assay is more and more being recognized as an animal welfare issue, and in addition is an unbelievably variable assay. AHI is partnering with CVB to develop a replacement assay. Because of collaboration between the regulated industry and CVB, two well-characterized monoclonal antibodies have been selected for further evaluation for the development of an enzyme-linked immunosorbent assay (ELISA) test. These efforts are ongoing.

Final issue: international trade. The U.S. releases 100 billion doses of vaccine every year, which are distributed domestically as well as worldwide. This dwarfs the scale of human vaccine distribution by orders of magnitude. Over the past few years, there have been increasing attempts by other countries to

try to restrict importation of U.S. products. Historically, restrictions were based on sanitary/phytosanitary concerns, but recently, restrictions appear to be protectionist. Some countries are no longer accepting CVB inspection certificates and are asserting that they need to do their own inspections. In other cases, countries will only accept their own inspections or an inspection from a partnering country. These restrictions are not based on science, but are intended to discourage the importation of products. Some countries/regions have done a very good job of "selling" their own regulatory system. For example, the E.U. has promoted their regulatory approach to emerging markets, and in so doing have implied that the U.S. regulatory system and U.S. products are inferior to those from the E.U. This is a growing concern. The U.S. needs to engage with global markets to promote the U.S. regulatory system for veterinary biologics as a high quality regulatory system designed to ensure the production of pure, safe, potent, and efficacious veterinary biological products.

ARS Recent Research Related to Biologics for Livestock—Progress and Status
Marcus Kehrli, USDA-ARS-National Animal Disease Center (NADC)

NADC's mission is to conduct basic and applied research on selected diseases and food safety pathogens of economic importance to the U.S. livestock and poultry industries.

Vaccine research at NADC includes work with a list of 20 pathogens they're doing some level of research with.

Only two diseases have been eradicated through human effort: smallpox—declared eradicated in May 1980, and rinderpest, declared eradicated by Food and Agriculture Organization (FAO) in October of 2010 and World Organisation for Animal Health (OIE) in May of 2011. Both efforts benefited through the use of modified live vaccines. Live vaccines in general provide stronger, longer lasting immunity as compared to inactivated products.

Dr. Kehrli provided updates with regards to research being conducted on vaccines for the following diseases:

- Brucella in bison, cattle, feral swine
- Tuberculosis in white tail deer and cattle
- Paratuberculosis in cattle, sheep and goats
- Salmonella in swine and turkeys
- Mannheimia haemolytica
- Pasteurella multocida
- Influenza A – swine
- Streptococcus suis in swine

Committee Business:

Resolutions:

- **Sustained Fiscal Year 2017 Funding for APHIS Influenza A Virus – Swine Surveillance Activities.** After a brief discussion, this resolution passed unanimously by verbal vote.
- **International Promotion of the U.S. Regulatory System for the Regulation of Veterinary Biological Products.** After a brief discussion, this resolution passed unanimously by verbal vote.
- **National Foot-and-Mouth Disease Preparedness**. After a brief discussion, this resolution passed unanimously by verbal vote.

Other business:

- A member of the committee asked if there was interest in combining the Committee on Pharmaceuticals with the Committee on Biologics and Biotechnology. He pointed out that he is a member of both committees, and that both had full agendas today. There was a brief discussion and members concluded that there is no apparent benefit to combining the two committees.

There was no further business and at approximately 4:30 p.m., the committee voted to adjourn.