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Marketing and Regulatory Programs

Animal and Plant Health Inspection Service

Veterinary Services

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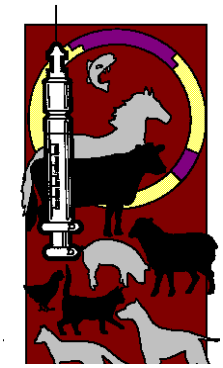
Vaccine Use Following Brucellosis and Pseudorabies Eradication



Center for Veterinary Biologics
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I. Summary

The Animal and Plant Health Inspection Service (APHIS) and its state and industry partners are approaching their goal of eradicating brucellosis and pseudorabies from the national cattle and commercial swine herds respectively. With that goal nearing, APHIS held discussions with stakeholders and the public regarding the need for continued production and use of vaccine after eradication has been declared, changes in the availability of diagnostic reagents and test kits, and possible changes to the biosecurity level assigned to the causative agents for both diseases. These discussions allowed stakeholders to identify issues and concerns they believed APHIS should consider before making any new biologics or biosecurity policies concerning brucellosis and pseudorabies.

II. Background

In October 2002, at a meeting held in St. Louis, MO, APHIS met with representatives of the veterinary biologics industry, producer groups, and animal disease researchers. Participants compiled a list of issues this group believed APHIS should consider when developing regulations and/or policy concerning the use of vaccine after the end of eradication programs for diseases such as brucellosis and pseudorabies. The group also suggested that APHIS seek additional input from state animal health officials, producer groups, and other interested persons prior to determining final policy.

To obtain additional input from these groups and other interested parties, the USDA APHIS Center for Veterinary Biologics (CVB) held a public meeting on June 10, 2005, in Des Moines, IA. Approximately 50 individuals from APHIS (staff, field, and laboratory personnel), the biologics industry, and various livestock producer groups attended. APHIS program staff presented brief updates concerning past and present vaccine use in the brucellosis and pseudorabies programs. Individuals from the following organizations provided comments for the record: National Pork Board, Iowa Farm Bureau Federation, Texas Animal Health Commission, National Institute for Animal Agriculture Brucellosis Eradication Task Force, Idaho Department of Agriculture, Animal Health Institute, and Association for Veterinary Biologics Companies. Representatives from the following biologics manufacturers provided comments: Colorado Serum Company, Fort Dodge Animal Health, Schering Plough Animal Health, and Boehringer Ingelheim Vetmedica. In addition, five letters from livestock officials were read for the record at the request of the sender. The letters were from the State of Oklahoma Department of Agriculture, Food, and Forestry; South Dakota Animal Industry Board; California Department of Food and Agriculture; National Cattleman's Beef Association; and the United States Animal Health Association.

The issues identified at the June 10, 2005, public meeting were essentially the same as those raised by the focus group invited to the 2002 St. Louis meeting.

III. Issues Identified

A. Brucellosis

All individuals who specifically addressed the issue of brucellosis vaccines (and each of the letters received from livestock officials) asked that APHIS make no changes to the current vaccine strategy for brucellosis. They believed vaccination should continue for the next several years. Reasons cited included:

- Wildlife reservoirs serve as a source of infection for domestic cattle herds in several states.
- Borders are porous and infected animals may be imported.
- The RB-51 vaccine is safe (no animal or human health risk).
- The vaccine does not interfere with serological tests used for surveillance.
- Maintaining immunity of the national herd is more important to producers than a questionable "free without vaccination" export provision.
- Vaccine is cost effective for producers that use it.
- A vaccine bank may not be cost effective because of short shelf life of the current product.
- APHIS has adequate controls in place governing vaccine use.

B. Pseudorabies

These issues included requests that APHIS:

- Allow production of pseudorabies virus (PRV) vaccine in the U.S. for the purpose of export following any decision to discontinue domestic use.
- Create a PRV vaccine stockpile.
- Allow widespread use and availability of diagnostics for detection of PRV.
- Work with the OIE to gain acceptance of the G1-deleted differential ELISA as an official test.
- Continue surveillance of feral swine as potential reservoirs of disease.

C. Biosecurity

Recommendations regarding biosecurity of declared eradicated agents were mixed. One representative of an agricultural organization asked that any agent, once eradicated, be placed on the select agent list and be subject to all biosecurity laws.

Representatives from the biologics industry asked that agents, once eradicated, not be automatically classified as select agents, but that each agent is considered separately based on risk. In regards to PRV, biologics industry representatives expressed the opinion that the virus not be placed on the select agent list because it is not a human health risk.

Another speaker advocated some controls on PRV, but emphasized that he did not believe it needed to be declared a select agent. This speaker suggested that APHIS determine who held the virus, track inventories, encourage disposal of unneeded virus stocks and samples after archiving useful isolates, and allow future movement only under permit.

Several speakers asked that APHIS continue to exclude the *Brucella abortus* vaccine strains from select agent requirements.

D. Production of Vaccine after Domestic Use is Discontinued

If a decision is made to discontinue vaccination for a particular disease, biologics manufacturers and several livestock officials stated the industry should be allowed to continue to manufacture products in the U.S. for export. The rationale for this request was as follows:

- The marketplace is global and products produced for export create domestic jobs.
- Vaccine production infrastructure would be maintained.
- Vaccine exported is of benefit to our trading partners and world animal health.
- In the event of an outbreak, vaccine production could be increased immediately, or serials diverted to domestic use.
- Imported vaccine may not be of the same quality as vaccine licensed by USDA.
- Adequate controls exist to prevent release of seed or challenge material from manufacturer's facilities; manufacturers have a good safety record.
- Adequate controls exist to prevent the domestic use of prohibited vaccine.

IV. Regulations and Guidelines

The Virus-Serum-Toxin Act of 1913, as Amended in 1985, the Code of Federal Regulations (9 CFR) Parts 101-118, and Veterinary Services Memoranda, address the regulations for preparation, sale, and licenses of biologics and vaccines used in animals. Part 105 addresses the circumstances under which biologics licenses may be revoked or terminated.

The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 and 9 CFR Part 121, Possession, Use, and Transfer of Biological Agents and Toxins, address the regulation of certain listed agents (select agents) that have been determined to have the potential to pose a severe threat to human or animal health or to animal products. The purpose of these regulations is to ensure the safe handling of such agents and to protect against the unlawful use of these agents.

CVB Notice No. 02-21, dated September 11, 2002, informed U.S. biologics licensees, permittees, and applicants that the CVB would accept license applications for the domestic manufacture of biologics for the prevention, diagnosis, or treatment of animal disease that are foreign to this country, as long as the biologic does not contain any infectious components that might endanger U.S. animals.

A National Center for Animal Health Programs (NCAHP) memorandum dated August 14, 2005, outlines the USDA APHIS Veterinary Services' animal health policy in relation to wildlife. This policy states that VS will seek measures to keep wildlife and livestock apart and to eradicate the disease from all potential reservoirs when eradication is deemed technically feasible. If eradication is currently not technically feasible, VS will seek to maintain separation of wildlife and livestock through cooperative efforts with wildlife agencies until research efforts can develop improved procedures to eliminate the disease from the wildlife/feral populations.

V. Current Status

A. Biologics Use: Brucellosis Program

Vaccination has been an integral part of the brucellosis eradication program since the first approved vaccine made its appearance in 1941. The current National Brucellosis Vaccination Policy, developed in 1996, supports proper calf-hood vaccination in high-risk herds and areas and supports the elimination of mandatory vaccination in all states. Also, the Brucellosis Emergency Action Plan (1997) recommends whole herd vaccination in herds considered at risk for exposure (e.g. those adjacent to known infected herds). In addition, the States set their own regulations on the mandatory use of vaccination in their native cattle and/or cattle imported into the state. These state regulations and policies vary considerably according to circumstances and risk to their herds.

B. Biologics Use: Pseudorabies Program

Data collected by the CVB indicate approximately 26.6 million doses of gene-deleted PRV vaccine were produced during FY 2005. The CVB does not track the number of doses of PRV vaccine exported, however sources at the manufacturers claim approximately 90 percent was exported. Additionally, a significant number of companion diagnostic test kits were produced and distributed both domestically and internationally in FY 2005.

The APHIS National Center for Animal Health Programs staff does not track domestic use of the PRV vaccine. They do know that some producers in a few states, including Iowa, Minnesota and North Carolina, continue to use the vaccine. This could explain the approximately 2.5 million doses manufacturers sell domestically.

C. Vaccine Reserve

Producers, state agriculture and APHIS Program officials all recognize the need for ready access to vaccine to control outbreaks of brucellosis and pseudorabies that may occur in the future. No decisions have been made to address the stockpile issue for either of these diseases.

D. Biosecurity (Select Agent Status)

Brucella abortus, the etiologic agent of bovine and human brucellosis, is currently classed as a select agent and those who possess, use, or transfer the agent are subject to regulations described in 9 CFR 121. *B. abortus* was deemed a select agent because it is highly infectious and easily transmitted by aerosol and thus could be used as an incapacitating agent. All biologics firms and research facilities that possess the agent are registered with either APHIS or the Centers for Disease Control. Select agent program oversight ensures adequate biosecurity for this agent.

The *B. abortus* vaccine strains (strain 19 and strain RB-51) are currently excluded from the requirements of the select agent regulations because the strains are attenuated.

The PRV is used in human and animal disease research. Therefore, stocks of virus exist in human and animal medical research facilities in addition to animal disease diagnostic laboratories. An APHIS permit is required for the transfer of the virus from one facility to

another.

Pseudorabies virus is not currently classified as a select agent.

E. Biologics Use in Wildlife

Brucellosis is endemic in wild bison and elk in the Greater Yellowstone area and affects cattle herds in Wyoming and Idaho. USDA has ongoing projects to mitigate the disease by vaccination. Strain RB-51 was used to vaccinate a few bison calves and yearlings corralled in Yellowstone Park. This effort will need to be expanded before any effects can be determined. The vaccine strain RB-51 has been determined to have poor efficacy in elk..

Eradication of pseudorabies virus in feral swine is not technically feasible at this time. Vaccines used in domestic swine have been shown to be useful in controlling pseudorabies in hunting reserve situations where the feral swine can be captured and vaccinated. However, there is no delivery system available to vaccinate free-roaming feral swine.

F. Domestic Production of FAD Biologics

Historical Perspective: A generation ago, biologics manufacturers voluntarily surrendered their licenses for classical swine fever (CSF) products and domestic manufacture of those products ceased. Master seeds used to produce CSF vaccine and antisera were also surrendered. These actions were appropriate at that time because of safety concerns with the live-virus CSF vaccines and the ability of the CSF virus to cause devastating outbreaks if it were accidentally released.

Current Situation: Vaccine production within the U.S. may be restricted or prohibited by the Secretary in order to protect the public health or safety or to prevent the sale of worthless, dangerous or harmful biological products. For example, this authority is used to prohibit the domestic manufacture of biologics for certain exotic diseases (e.g. foot-and-mouth disease).

Domestic manufacture of biologics for exotic diseases is allowed as long as the biologic does not contain any infectious components that might endanger U.S. animals.

VI. Future Expectations and Strategies

A. Brucellosis Program

While the ultimate goal is to eliminate the need for vaccination of livestock, it is probably not feasible in the next five years. Therefore, it is expected that vaccination will be used to control any final outbreaks and to protect cattle herds exposed to wildlife reservoirs in the Greater Yellowstone Area for as long as those reservoirs exist. Vaccine will also play a role in the control and eradication of brucellosis from those wildlife reservoirs.

The future program, beyond eradication of brucellosis in the national cattle and swine herds and the elimination of the disease in wildlife will be one of preparedness. A ready supply of vaccine will be needed in the event of outbreaks in cattle or the reappearance of brucellosis in wildlife reservoirs that again place cattle at risk.

B. Pseudorabies Program

It is expected that vaccine could also be used to control future outbreaks of pseudorabies. Since the virus exists in feral swine populations throughout the United States, sporadic outbreaks in commercial swine may occur. Producers and state animal health officials will need prompt access to vaccine to quickly control such outbreaks.

Licensed diagnostic test kits that differentiate vaccine titers from natural exposure will be needed for as long as vaccine is used whatever the circumstances. Diagnostics will also be needed long-term for surveillance testing.

C. Vaccine Reserve

In the future when domestic vaccine use is discontinued, vaccine needs for outbreaks could be met by APHIS maintaining a bank or stockpile of either vaccine or antigen. The need could also be met by contracts with one or more manufacturers requiring that firm to maintain a specified number of doses that could be immediately diverted to domestic use. The latter method assumes that manufacturers will not be prevented from producing vaccine for export after domestic use is discontinued.

D. Biosecurity Issues

As previously stated, *Brucella abortus* is currently classified as a select agent and the vaccine strains (RB-51 and Strain 19) are excluded from the select agent regulations. This is not expected to change. If additional vaccine strains are developed, it is expected that they, too, would be excluded from regulation if data are available to show that the new strain is not a severe threat to human health.

No decision has been made to classify PRV as a select agent. There are reasonable arguments for and against adding PRV to the select agent list. On one hand, at some point PRV will be eradicated and there is a reasonable expectation on the part of producer groups that APHIS will implement some controls to prevent misuse or unintended release of the virus from facilities that could cause an outbreak. Placing the virus on the select agent list would provide a mechanism for APHIS to control possession and use of the virus. On the other hand, PRV does not appear to meet the criteria used to place other agents on the select agent list. The virus is not a threat to human health. Pseudorabies is primarily a disease of newborn pigs; it does not cause devastating disease in all ages of swine. Therefore, the virus is unlikely to be used as a terror threat. Vaccines and diagnostics are available to control outbreaks. In addition, no documented reports of accidental release from a research, diagnostic, or manufacturing facility causing an outbreak in swine, indicate that standard biosecurity procedures are adequate for PRV.

If PRV is classified as a select agent, it is reasonable to assume that the gene-deleted vaccine strains would be excluded from the regulations because they pose no threat to human or animal health.

A decision to classify PRV as a select agent could be made when the disease is declared eradicated from domestic swine or at some time in the future after the virus is eliminated from feral swine populations.

E. Wildlife Issues

The National Animal Disease Center and APHIS VS are conducting a study to evaluate a genetically engineered RB-51 vaccine strain that may prove more efficacious in elk. While it appears theoretically possible to eradicate brucellosis from wildlife, the effort is expected to take many years.

Eradication of pseudorabies in swine is more problematic. Because of the difficulty in catching and restraining feral swine, there is a need to develop an oral PRV vaccine delivery method that is effective and environmentally safe. It may be decades before commercial swine operations are free from the risk of outbreaks from feral swine.

Measures that keep the wildlife (and feral animals) separate and apart from domestic livestock will continue until eradication of brucellosis and pseudorabies from these reservoirs is accomplished. If eradication of brucellosis and/or pseudorabies from these reservoirs is not deemed feasible, measures that keep the wildlife (and feral animals) separate and apart from domestic livestock must continue indefinitely and be included as part of the state's disease management program.

F. Domestic Production of Brucellosis and Pseudorabies Vaccines after Eradication

To meet the need for some level of biologics use, APHIS will consider allowing biologics manufacturers to continue, with certain stipulations to ensure biosecurity, to manufacture products for prevention and diagnosis of *Brucella abortus* and PRV after eradication in domestic animals in the United States has been accomplished. This would provide continued availability of licensed biologics in the event of a disease outbreak without presenting significant risk to the animal or human populations, and without significantly affecting the manufacturers' desire to pursue a global market for these products.

G. Other Agents

Decisions concerning vaccine production and use for diseases that are eradicated in the future will be addressed on a case-by-case basis.

VII. Timeline

Near Term Actions (Next 6 months):

- Decision to allow domestic production for export of brucellosis and PRV biologics.
- Communication of decision to biologics manufacturers.

Intermediate Term Actions (Next 1-3 years or at time PRV is eradicated from commercial swine):

- Decision on select agent status of PRV following eradication from the national herd; development of biosecurity requirements for non-biologics facilities.
- Development of guidelines on domestic production of PRV vaccines (biosecurity requirements) and license restrictions.

Long Term Actions (Next 4-20 years or until such time as brucellosis and PRV are eradicated from wildlife):

- Continue cooperative vaccine projects with the goal of eradicating brucellosis and PRV from wildlife and/or feral animals.

Upon successful eradication from wildlife reservoirs:

- Revisit biosecurity requirements and/or select agent status of PRV.