Animal and Plant Health Inspection Service

Veterinary Services

1400 Independence Ave, SW

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.110

TO: Veterinary Services Leadership Team
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

FROM: Jack A. Shere /s/ Jack Shere June 30, 2017
Deputy Administrator

SUBJECT: Label Warnings Concerning Bovine Rhinotracheitis Vaccine, Modified Live Virus, and Bovine Virus Diarrhea Vaccine, Modified Live Virus, for Pregnant Cows or Calves Nursing Pregnant Cows

I. PURPOSE

This memorandum provides Center for Veterinary Biologics (CVB) guidance for label warnings and for claiming exemptions to the warning requirements against the use of bovine rhinotracheitis (IBRV) vaccine, modified live virus, and bovine virus diarrhea (BVDV) vaccine, modified live virus, in pregnant cows or in calves nursing pregnant cows.

II. CANCELLATION

This memorandum cancels Veterinary Services (VS) Memorandum No. 800.110 dated October 18, 2004.

III. BACKGROUND

Title 9, *Code of Federal Regulations* (9 CFR), section 112.7(e)(1) requires labels for IBRV and BVDV vaccines containing modified live virus to bear the following warning: “Do not use in pregnant cows or in calves nursing pregnant cows.” The Administrator, Animal and Plant Health Inspection Service, may grant an exemption to this requirement under 9 CFR 113.4(a), provided that such a vaccine has been shown to be safe for such use. This memorandum provides guidance concerning the data needed to obtain the exemption. The data may also be used to support the label claim “for use in pregnant cows or in calves nursing pregnant cows.”

To obtain the exemption to the warning statement and to support the label claim (above), supporting studies should be conducted as in section IV.

IV. GUIDELINES

Only heifers and cows that are confirmed pregnant should be included in the study. All animals should be vaccinated with an appropriate single or multifraction test vaccine. Animals must be vaccinated in accordance with product labeling, including, if recommended, a pre-breeding vaccination. If vaccination prior to breeding is not required, all animals must be seronegative for virus prior to administration of the test vaccine. Studies that involve only the vaccination of calves that are nursing pregnant heifers or cows will not be acceptable for claiming the exemption. Clinical studies should be conducted in accordance with VS Memorandum No. 800.301.

A. Study Design

1. *Animals* – At least 1,200 pregnant heifers and cows must be included in the study. Animals should be divided into three groups of 400 animals each on the basis of stage of pregnancy; i.e., the first, second, or third trimester.

    a. Three separate studies may be conducted; however, at least 400 animals are needed for each stage of pregnancy.

    b. All animals included in the study must be followed through parturition.

2. *Randomization* – Randomly divide each group (trimester) into two groups (vaccinates and controls), each containing 200 animals.

    a. Inoculate animals in the vaccinate group with the modified live virus test vaccine.

    b. Inoculate animals in the control group with inactivated vaccine or phosphate buffered saline.

    c. The groups should be adequately separated so as to prevent the controls from being exposed to vaccinates that may be shedding vaccine virus.

B. Vaccine

Vaccine used in the study should be formulated in accordance with the filed Outline of Production. If vaccination prior to breeding is recommended, the identity of the vaccine used for the pre-breeding vaccination should be specified in the report and on the labeling.

C. Data

For each group, the calving rate, the health status of the calves up to 4 weeks post-partum, and the Clopper-Pearson 95% confidence interval for the aborting fraction should be determined and summarized in the study report.

1. *Abortions* – Animals that do not deliver a live calf will be counted as abortions, cause unknown. Abortions due to diagnosed causes other than BVDV or IBRV, as applicable, will be excluded from the data analysis.

   a. Aborted calves should be necropsied and the results included in the study report.

   b. The study must be repeated for any trimester group in which the rate of abortion due to any cause exceeds 5%.

   c. An exemption may not be approved if the rate of abortion due to IBRV or BVDV exceeds 0.5% in any trimester group.

2. *Fetal Infection, BVDV* – To detect BVDV capable of causing fetal infection without causing abortion, pre-suckling serum samples from at least 100 randomly chosen calves born from the second and third trimester pregnancy groups (50/group) should be tested for antibody to types 1 and 2 BVDV and to IBRV; an exemption may not be approved if any animal has a positive test.

3. *Adverse Events Monitoring* – The CVB may monitor adverse events reported to the company and compare the number of adverse event reports per number of doses of vaccine marketed that have been received by the firm after the exemption to the number of adverse event reports per number of doses of vaccine marketed that have been received by the firm prior to the approval of the exemption. If evidence of safety problems is encountered, the CVB will take appropriate action(s).

D. Labeling

With the exemption, labeling (including the circular) should include a statement that the vaccine may be used in pregnant cows and calves nursing pregnant cows, with a brief description of the study and a summary of the results.

1. *Pre-breeding Vaccination* – If vaccination prior to breeding is required, the recommended product and dose should be specified on the label. Multifraction vaccine(s) produced by the same manufacturer may be recommended provided that they are produced using the same master seed virus, master cell stock, and serial release titer as the test vaccine. Wording acceptable to the CVB is "This vaccine may be used in pregnant cows or calves nursing pregnant cows provided they were vaccinated, pre-breeding, with <insert product name>."

2. *Warnings* – Labeling must also bear the following statement concerning residual risk; see also 9 CFR 112.7(e)(3): "Fetal health risks associated with the vaccination of pregnant animals with this vaccine cannot be unequivocally determined during clinical trials conducted for licensure. Appropriate strategies to address the risks associated with vaccine use in pregnant animals should be discussed with a veterinarian."

3. *Aborting Fractions* – Because treatment groups may not have been commingled during the study, inferences concerning any relationship between the calculated aborted fraction(s) for the groups must be reviewed by the CVB.

V. ACTION

Section IV presents the simplest design for a minimally acceptable study. If a firm wishes to design a more complex study; e.g., a study that will support between group inference (i.e., that includes replication to prevent confounding of treatment and housing), they may do so. Protocols should be submitted to the CVB for review prior to the initiation of any study. Upon successful completion of a study and acceptance of the data, the CVB will approve an exemption to the warning requirement under 9 CFR 112.7(e)(1).

VI. IMPLEMENTATION/APPLICABILITY

This memorandum is effective immediately.