CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 24-13

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

FROM: Geetha Srinivas, DVM, PhD.
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Date: 2024.08.28 16:04:45 -05'00'

SUBJECT: Field Studies with Nonviable, Non-replicating Veterinary Vaccines Targeting Highly Pathogenic Avian Influenza in Livestock

I. PURPOSE

The purpose of this Notice is for the Center for Veterinary Biologics (CVB) to provide an update to interested parties regarding veterinary biologics product license applications for veterinary biological products used to vaccinate livestock for Highly Pathogenic Avian Influenza (HPAI) H5N1, clade 2.3.4.4b. This Notice includes an update on field studies to support licensure.

II. BACKGROUND

The United States Department of Agriculture (USDA), Animal and Plant Health Inspection Service (APHIS), National Veterinary Services Laboratories (NVSL) first confirmed H5N1 in U.S. dairy cattle on March 25, 2024. NVSL made the recent HPAI H5 clade 2.3.4.4b sequence available as noted in Notice 24-06. CVB previously posted a related request for information on H5 HPAI vaccines and status of development in Notice 24-09 and related information on vaccine efficacy considerations in Notice 24-11.

III. ACTION (or POLICY)

USDA acknowledges the veterinary biologics industry's interest in the development of vaccines for potential use in livestock or other animal species against H5 HPAI. CVB is providing the following updates but also noting that this is a rapidly evolving situation. These points should be considered current unless this CVB Notice is cancelled or superseded.

1. Previously, CVB indicated that all studies, even those not involving virus challenge, were to be conducted in containment facilities regardless of risk profile.

2. CVB is now accepting submissions for field studies to support conditional or full licensure of nonviable, non-replicating vaccines.

3. Field studies to support licensure of nonviable, non-replicating vaccines may be conducted outside of containment without terminal disposal of milk and other commodities. These studies should follow the requirements found in title 9, *Code of Federal Regulations*, part 103.3 including State Animal Health Official permission. Additionally, firms are requested to include an acknowledgment (formal or informal) from the USDA Area Veterinarian in Charge (AVIC) in supporting documentation.
    a. Note that manufacturers must maintain adequate records relative to the disposition of each animal administered experimental biological products for a minimum of 2 years from the date of first vaccination, including all requirements outlined in 9CFR 103.2.
    b. Additionally, a VS Form 1-27 issued by an USDA Accredited Veterinarian will be needed to move cattle to slaughter for up to 2 years from the date of first vaccination. Additional restrictions may apply.
    c. A minimum withdrawal time must be reviewed by CVB prior to conduct of field studies. Proposals should focus on the formulation of the proposed vaccine and follow the guidance in Veterinary Services Memorandum 800.51.
    d. Vaccine manufacturers must track vaccine shipments, use, and disposal. Diversion of the vaccine for any other purpose is prohibited. Tracking information must be available to the CVB upon request.
    e. CVB will consider conditional licensure for vaccines for lactating dairy cattle with either separate or combined field efficacy and field safety study data from those target animals. Studies should be planned to maximize both efficacy and safety evaluations. As this is a high-profile emerging disease, in addition to evaluation of reasonable expectation of efficacy, a full and complete examination of the safety of these experimental vaccines is warranted.
    f. As noted in Notice 24-11, if USDA authorizes HPAI vaccine use or stockpile purchasing, preference may be given to products that best fit national program objectives. Proposals for other target animals should be submitted to the CVB in advance of study initiation, and studies are conducted at the firm's risk. At the time of this CVB Notice, USDA has not authorized the use of H5 vaccines in the United States. Any products that are licensed will carry a restriction prohibiting U.S. sale, distribution, and use until further notice.

4. Protocols should be submitted and should include comprehensive milk and serum testing. Milk and serum from lactating animals should be sampled from a subset of the study population, including controls, pre-vaccination and at appropriate time points post vaccination.
    a. Testing of serum should focus on antibodies to the H5 hemagglutinin using a hemagglutination inhibition assay. The testing results will be evaluated for reasonable expectation of efficacy.

b. Testing of milk should evaluate for residual vaccine components and antibodies using an ELISA or similar assay.
c. Consider evaluating serum samples at the same time points as the milk samples in order to generate correlative data, but this is not a requirement.
d. Any injection site reactions or other adverse events must be fully investigated, evaluated, and submitted to the CVB as stated in Veterinary Services Memorandum 800.204.

5. Studies utilizing live vaccines or challenge with HPAI will require containment of animals and terminal disposal. Contact CVB for further discussion.

Parties interested in licensing an H5 HPAI vaccine should contact CVB for further guidance. Refer to Title 9, Code of Federal Regulations, Chapter I, Subchapter E; Veterinary Services (VS) Memorandum 800.50, Basic License Requirements and Guidelines for Submission of Materials in Support of Licensure; and VS Memorandum 800.101, U.S. Veterinary Biological Product Permits for Distribution and Sale. This information is available on the CVB website: https://www.aphis.usda.gov/veterinary-biologics/regulations-guidance.

IV. IMPLEMENTATION/ APPLICABILITY

Applications and supporting materials may be submitted to the CVB-Policy, Evaluation, and Licensing for review effective immediately. If your firm is not portal enabled, you can email responses using the subject line: "Products Targeting HPAI" to the USDA Center for Veterinary Biologics at CVB@usda.gov.