USDA
United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

Center for Veterinary Biologics

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CENTER FOR VETERINARY BIOLOGICS NOTICE NO. 15-13

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

FROM: Byron Rippke
Director

BYRON RIPPKE
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SUBJECT: Option to Remove Back-titration Hamsters from In Vivo Potency Tests for Leptospira Serogroups Canicola and Icterohaemorrhagiae

I. PURPOSE

The purpose of this notice is to inform interested parties that the Center for Veterinary Biologics (CVB) will allow an exemption from the titration requirement in vaccination-challenge potency assays for Leptospira Serogroups Canicola and Icterohaemorrhagiae. Removal of the back-titration hamsters could reduce animal use by 50% when potency testing these two fractions.

II. BACKGROUND

The codified potency tests for Leptospira Canicola Bacterins and Leptospira Icterohaemorrhagiae Bacterins are hamster vaccination-challenge assays described in title 9, *Code of Federal Regulations* (9 CFR), parts 113.102 and 113.103 respectively. These tests have been targeted by the CVB as part of our ongoing commitment to refine, reduce, and replace animal testing.

Currently, a valid test requires ≥80% (8/10) of challenge control hamsters to succumb to disease and an LD_{50} between 10 and 10,000. The minimum LD_{50} requirement has always been met if at least 80% of challenge controls succumbed to disease; the back-titration hamsters are not required to confirm a minimum challenge dose is administered. The maximum LD_{50} constraint has been based on 1) reports that subpotent bacterins may occasionally test potent when ≥10,000 LD_{50} is administered and 2) historical concerns that a potent serial may be deemed subpotent when challenged with a higher concentration of *Leptospira* than normally seen in the field.

Tests were conducted at the CVB to evaluate the risk associated with the removal of the maximum LD_{50} limit. The CVB could not identify an increased risk of releasing a subpotent vaccine. A small risk was identified that some potent bacterins may be deemed unsatisfactory when the challenge LD_{50} exceeds 10,000. The risk will vary by product.

III. ACTION

Firms may request an exemption from the titration requirement for the vaccination-challenge potency assays for Leptospira Serogroups Canicola and Icterohaemorrhagiae when using the CVB supplied strains. The CVB will accept the following alternative in the Outline of Production:

Modified 9 CFR Vaccination-Challenge Leptospira Assay

This modified approach allows a one-stage vaccination-challenge assay *without* back-titration hamsters followed by an option to test by the 9 CFR potency assay *including* back-titration hamsters. Details are as follows:

1) For the initial test, 10 vaccinated hamsters and 10 challenge control hamsters will be tested according to the 9 CFR specifications, except the LD_{50} of the challenge will not be monitored.

2) Results for the initial test shall be evaluated as follows:
    a. At least 8 of 10 challenge control hamsters must succumb to disease for a valid test. If <8 challenge control hamsters succumb to disease, the test is declared a "NO TEST" and the vaccination-challenge assay *without* back-titration hamsters is repeated without prejudice.
    b. If ≥8 of 10 vaccinates survive in a valid test, the serial is declared "SAT" and no additional testing is necessary.
    c. If ≤2 of 10 vaccinates survive in a valid test, the serial is declared "UNSAT" and no additional testing will be conducted.
    d. If 3-7 of 10 vaccinates survive in a valid test, the serial may be declared "NO TEST" and tested by the complete codified 9 CFR method. Any serials not tested by the 9 CFR method will be declared UNSAT.

3) Special instructions concerning testing by the complete codified 9 CFR test, which *includes* back-titration hamsters, are as follows:
    a. All tests in which the challenge exceeds 10,000 LD_{50} will be considered invalid.
    b. The results from the complete codified 9 CFR test will be evaluated independently from the initial test. The number of survivors in the complete codified 9 CFR retest will not be combined or averaged with the number of survivors from the initial test to determine the potency of a serial.

The potency assays outlined in 9 CFR 113.102 and 113.103 remain acceptable if a firm prefers not to request an exemption from the titration requirement. If a firm chooses to test by the codified methods, all tests in which the challenge exceeds 10,000 LD_{50} will be considered invalid in accordance with 9 CFR 113.102 and 113.103.

IV. IMPLEMENTATION

According to 9 CFR 113.4, licensees and permittees must request an exemption to the codified hamster potency tests if they are interested in using an alternate approach. The Outline of Production must specify the titration exemption for each fraction. This policy is effective immediately.