USDA
United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

1400 Independence Ave, SW

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.201

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

FROM: Jack A. Shere
Deputy Administrator

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Date: 2018.01.25 13:11:51 -05'00'

SUBJECT: General Licensing Considerations: Backpassage Studies

I. PURPOSE

This memorandum provides guidance related to title 9, *Code of Federal Regulations*, parts 102.5 and 104.5. It provides information and recommendations about the design and conduct of backpassage studies to support an application for a U.S. Veterinary Biological Product License or U.S. Veterinary Biological Product Permit for Distribution and Sale.

Although this memorandum represents current policy regarding reversion to virulence studies, it does not confer rights for, or on, any person and does not operate to bind Animal and Plant Health Inspection Service (APHIS) or the public. An alternative approach is acceptable if such approach satisfies the requirements of the applicable statute, regulations, or both.

II. CANCELLATION

This memorandum replaces Veterinary Services (VS) Memorandum No. 800.201 dated June 25, 2008.

III. BACKGROUND

The Center for Veterinary Biologics-Policy Evaluation and Licensing (CVB-PEL) requests that license and permit (for distribution and sale) applicants conduct backpassage studies to evaluate the stability of Master Seeds for conventional modified live or live recombinant vaccines to provide assurance that such vaccine micro-organisms will not revert to virulence when administered to the host animal. Live vaccines are those that may be capable of replication in the target animal, stimulate a useful immune response, and generally cannot be completely characterized by chemical and physical tests alone.

APHIS is a member of the International Cooperation on Harmonization of Technical Requirements for the Registration of Veterinary Medicinal Products (VICH). This policy is consistent with VICH requirements for licensure of live vaccines. VICH Guideline (GL) 41, *Examination of live veterinary vaccines in target animals for absence of reversion to virulence,* outlines the requirements to demonstrate a lack of reversion to virulence.

One objective of VICH is to promote harmonization of technical regulatory requirements for veterinary medicinal products among regulatory agencies in different countries. APHIS is committed to seeking scientifically based harmonized technical requirements for veterinary biological products. Developed under the principles of the VICH, VICH GL 41 provides a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the relevant regulatory authorities for reversion to virulence studies. VICH members developed this guideline with consideration of the current practices in the European Union, Japan, and the United States, together with those of Australia and New Zealand. The results of a study conducted as per VICH guidelines, or per the guidelines in VS Memorandum No. 800.201, should be acceptable to APHIS to demonstrate lack of reversion to virulence.

Backpassage studies consist of successively propagating vaccine Master Seed through a series of backpassages *in vivo*. Applicants administer the Master Seed microorganism to a group of susceptible host animals and, after an appropriate incubation time, recover the microorganism from these animals and administer it to a second group of susceptible host animals. Applicants should conduct a minimum of five such successive passages.

IV. GUIDELINES

A. General

1. *Study Protocols.* Applicants should submit a detailed protocol, including the criteria for determining reversion, for CVB-PEL review before initiating a backpassage study.

2. *Preliminary Data*. The CVB recommends that applicants submit preliminary data from studies conducted to evaluate the route of administration and procedures for recovery and to assess the expected rate of recovery of the vaccine microorganism from test animals with the proposed protocol. The CVB-PEL will consider the backpassage requirement fulfilled when the applicant confirms preliminary data indicating that the applicant cannot recover the vaccine microorganism from vaccinates by using a group of 10 animals in a follow-up study performed as outlined in section IV.B of this memorandum.

3. *Passage Procedures*. In progressing from one backpassage to the next, applicants may concentrate recovered material between passages but APHIS prohibits in vitro propagation between passages.

4. *Study Animals*. Applicants should conduct the backpassage studies in the most susceptible species of animals recommended on the label. Applicants must conduct the study in animals of the most susceptible age, regardless of minimum age recommendations on the label. These test animals should also be susceptible (seronegative) to the vaccine microorganism being tested. Applicants must include a justification for the species, age, and sex of the test animals in the protocol submitted for review.

5. *Combining Backpassage Studies with Shed-and-Spread Studies*. If the route of administration for backpassage studies determined from preliminary work is the same as the route of administration recommended on the label, applicants may expand backpassage studies to also collect data on shed and spread of the vaccine microorganism; otherwise, the CVB-PEL requires a separate shed-spread study.

B. First Backpassage

1. *Route of Administration.* Administer the vaccine Master Seed to a group of host animals by the route most likely to lead to replication and reversion of the microorganism to virulence.

2. *Numbers of Animals.* Use two to five animals, as needed, to ensure reisolation and continued backpassage (see table in VICH GL 41 on probability of reisolation). Use ten animals to confirm failure to recover the vaccine microorganism from a preliminary study (see IV.A.2.).

3. *Dosage.* Administer test animals at least a typical vaccine dose (not an immunogenicity test dose). The applicant should formulate a typical vaccine dose at a titer that is above the targeted release dose of the product and includes overage for the expected loss of titer over dating and testing variation.

4. *Recovery of the Microorganism.* After a period consistent with the pathophysiology of the progression of the disease in a naturally infected animal, attempt to recover the vaccine microorganism from the most appropriate tissues or secretions collected from treated animals.

C. Successive Backpassages

1. *Passage Procedures.* Administer recovered material (pooled material is acceptable) from animals in the preceding treatment group to animals in successive groups by the same route as in the first passage.

2. *Number of Animals for Each Successive Passage.* Based on the expected rate of recovery, treat two to five animals as needed to provide a high probability of reisolation.

3. *Observations.* Observe treated animals for clinical signs indicative of reversion of the vaccine strain to virulence. Test operators should assess clinical signs that indicate administration of the material caused adverse effects to the animal.

4. *Number of Passages*. Make at least five backpassages (four successive backpassages beyond the first backpassage).

5. *Maintenance Period.* Maintain test animals from the last backpassage group for at least 21 days after administration of the recovered microorganism, unless otherwise justified.

6. *Characterization.* Characterize the microorganism isolated from the last backpassage phenotypically and/or genotypically and compare it with the Master Seed to evaluate genetic stability and reversion to virulence.