USDA

Animal and Plant Health Inspection Service

Veterinary Services

1400 Independence Ave, SW

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.204

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

FROM: for Jack A. Shere
Deputy Administrator

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SUBJECT: General Licensing Considerations: Field Safety Studies

I. PURPOSE

This memorandum provides guidance to applicants for developing target animal field safety data to support an application for a U.S. Veterinary Biological Product License or U.S. Veterinary Biological Product Permit for Distribution and Sale. Regulatory reference can be found in title 9, *Code of Federal Regulations* (9 CFR), parts 102.5 or 104.5, respectively.

II. CANCELLATION

This memorandum cancels Veterinary Services (VS) Memorandum No. 800.204 dated March 16, 2007.

III. BACKGROUND

Licensing considerations provide guidance to applicants concerning the development of data in support of license applications and assist the Center for Veterinary Biologics-Policy, Evaluation, and Licensing (CVB-PEL) in maintaining uniformity and consistency in the review of license applications. General Licensing Considerations address basic principles that have general application in the licensing of products. This document addresses the basic principles for conducting observational field safety trials (FST), which usually satisfy the safety requirements for licensure of biologics administered to healthy animals. More rigorously designed safety studies are sometimes indicated, and they are not covered by this document.

The objective of a typical target animal FST is to assess the safety of the product in its target population under the conditions of its intended use. The goal of the FST is to detect the types of adverse events that may occur with sufficient frequency to be seen in a trial of this scale. The FST is an essential clinical component of the prelicensing process, supplementing smaller preclinical experimental studies, but not replacing ongoing post-marketing surveillance. The FST also may be required to support changes in the recommended administration of licensed products.

IV. GUIDELINES

A. General Requirements. Safety studies must meet the following general requirements:

1. *Permission Required.* All field safety studies must meet the requirements set forth in 9 CFR 103.3 and VS Memorandum No. 800.67. Applicants must obtain permission to conduct a field safety study from the CVB prior to shipping the product to the test sites. See VS Memorandum No. 800.50 for guidance on submitting a field test request to the CVB.

2. *Planning and Execution.* Applicants should plan, execute, and document field safety studies in accordance with the general guidelines provided in VS Memorandum No. 800.200.

B. Experimental Product. Applicants should test more than one serial (numbered lot) of product. The experimental product that applicants use in field safety studies should be produced:

1. *In Accordance With the Filed Outline of Production.* The experimental (prelicense) product the applicant uses for generating field safety data must accurately represent the product that the firm will produce once a product license is granted. The applicant is responsible for establishing the validity of the experimental product used to demonstrate field safety.

2. *In Licensed Production Facilities.* Produce the experimental product in licensed production (not research) facilities, in accordance with filed facility documents.

3. *At, or Above, Release Potency.* The potency of the experimental product should be at, or above, the minimum potency specified in the Outline of Production for serial release.

4. *Largest Combination.* If an applicant has multiple related products (differing only in the number/combination of antigens) being considered for licensure, the applicant should conduct the field safety study with the largest antigen combination. Additional field safety studies are typically not required for fall-out products (i.e., products identical to the tested product except for the removal of one or more antigens) unless specific safety concerns arise.

C. Experimental Protocol. In addition to the general information described in VS Memorandum No. 800.200, field safety study protocols should contain the following specific information:

1. *Study Design.* Field safety studies generally may be satisfied with uncontrolled observational trials of the product under typical field husbandry conditions. The object of such trials is to detect adverse events of unexpected type or frequency that might indicate the need for further investigation.

2. *Geographic Locations.* Applicants should carry out studies in multiple geographic regions. Typically, three distinct regions of the United States are required. When applicable, the applicant should test the product under various conditions of husbandry. Reviewers may use their discretion regarding the acceptability of any proposed combination of sites and must take into account individual circumstances. Reviewers may consider data generated in countries other than the United States, on a case-by-case basis, to fulfill requirements for one of the geographic regions.

3. *Type of Animals.* Applicants should describe the age, breed, sex, pregnancy and/or lactation status, and any other distinguishing features of animals used in the test. All types of animals included in label recommendations should be included in the study.

4. *Number and Age of Animals.* An adequate number of animals of the minimum recommended age should be included in the study. The number of animals may depend on the species and type of animal industry. The minimum age of animals in the safety study should be consistent with the age of animals used in efficacy studies. (If the age of the animals in the efficacy and safety studies is not consistent, the minimum recommended age on labeling will be the older age.) For products intended for use in poultry, production livestock, or aquaculture, all animals in the safety study should be of minimum age. If a product is intended for production livestock species but will be used in animals of breeding age, at least one-third of the animals in the safety study should be of minimum age. Likewise, at least one-third of the animals should be of the minimum age in safety studies of products intended for use in companion animals or horses.

5. *Product Administration.* Test operators should administer the product according to the product label, including the administration of multiple doses and/or alternate routes of administration. Test operators should test each recommended vaccination regimen and each product serial in an equivalent proportion of animals in each geographical region. The protocol should include the number of animals test operators will vaccinate by each regimen and with each serial in each region.

6. *Injection/Administration Sites.* Under select circumstances (e.g., transdermal or ballistic administration, etc.), the CVB may require evaluation of different administration sites (e.g., neck vs. gluteal in large animals, thigh vs. lumbar in companion animals).

7. *Passive vs. Active Immunity.* When a product is recommended for use both in adults and in neonates, for protection of neonates (i.e., has label claims for passive and active immunity), safety must be demonstrated in adults and neonates.

8. *Observation Period.* The protocol should include the frequency and duration of observations, personnel making observations, and the follow-up response to an adverse event. For live products, an acceptable period of observation must take into account the incubation period associated with the live organism(s).

   A qualified investigator (e.g., veterinarian or trained specialist) should actively observe animals in the study at key study points *in addition to* the immediate post-vaccination period. The study protocol should specify the key points.

9. *Reporting Forms.* Provide copies of the reporting form(s) and the instructions that will be issued to field investigators and (if applicable) animal owners. The reporting system must provide for individual animal identification (or group identification for poultry and aquaculture).

10. *Disposal*. The disposal of all animals intended for food used in field safety studies must be in accordance with 9 CFR 103.2.

D. Considerations for Specific Animal Species

1. *Herd animals (mammalian).* For studies where the enrolled animals are maintained post-vaccination in pens or groups:

   a. Test operators should routinely observe animals for adverse events at the intervals specified in the study protocol. It is permissible to conduct these evaluations on a group basis (i.e., do not need to individually handle each animal), provided the group size is small enough to allow adequate observation of each animal within the group.

   b. A qualified investigator should individually examine (including palpation of the injection site) each animal *at least* once after each immediate post-vaccination period. The study protocol should specify the timing of this examination, which should occur when injection site reactions are most likely to be evident. A qualified investigator should continue to examine animals exhibiting palpable injection site reactions at appropriate intervals until the reaction has resolved. The investigator should measure and report the size and duration of all injections site reactions. The investigator should summarize this information in the report and individual studies summary (ISS) and submit it in the electronic data according to CVB Data Guidelines.

2. *Poultry.* When groups are maintained in houses without unique animal identification:

   a. Test operators may use daily mortality sheets as documentation for the FST. The applicants should summarize the information from these sheets in the report and submit it as indicated in section IV.F.5.

b. Test operators generally use comparison houses/farms to evaluate normal mortality rates (formerly referred to as control houses/farms). Acceptable comparisons may utilize data from other houses placed concurrently, data from the same house during the periods immediately before and after placement, historical data from the same house, or other benchmarks used by the poultry company. Historical data should take into account seasonal disease fluctuations. The FST protocol should specify the comparison group.

c. Slaughter data from broilers will only be required on a case-by-case basis. These data may be required if the condemnation lesion is a poultry specific disease characteristic or bears significance to vaccine safety or public health.

d. Daily observation records are required for at least 21 days after vaccination.

e. Studies should compare the typical vaccination regimen of the house/farm site to a regimen with the test vaccine. Therefore, depending on the vaccine, the study could compare vaccination to a lack of vaccination or to vaccination with another product. The report must provide the site's typical vaccination regimen.

f. It is acceptable to use more than three companies or geographical regions or addresses for the FST. A site may include several houses on a farm or several farms for one company. Test operators must include specific farms used in the field safety study in the final field safety study report, but it is not required to identify specific farms in the field safety study protocol. Test operators may use the same region for multiple sites if husbandry differs.

g. It is possible to offer poultry farmers a preliminary trial to evaluate domestic test vaccines with authorization if the test vaccine shares similarities to the firm's licensed products. The preliminary evaluation is considered part of the final FST, though, and test operators must report results. If a small number of birds is included in the preliminary trial, test operators may supplement these results with data generated with additional vaccinated birds.

h. Licensure of niche avian products requires substantially fewer birds than products designed for commercial broiler or layer operations. Examples of niche products include products for pet birds or pigeons.

3. Aquaculture species

a. Test operators may use daily mortality sheets as documentation for the FST. Test operators should summarize the information from these sheets in the report and submit it as indicated in section IV.F.5.

b. Test operators may provide information on typical mortality rates from comparison tanks.

c. Applicants may design the study so that they enroll all of the fish of minimum size/age at one site rather than having such fish represented at all sites. Applicants should include and justify the size/age of vaccinated fish in the protocol.

d. Daily observation records are required for 28 days after vaccination to allow time to determine if fish will survive and return to normal feeding habits.

e. If a product is recommended for use in multiple species, applicants must demonstrate field safety in each species.

f. The number of distinct geographical regions is determined by the environmental conditions, which may limit where fish are raised.

g. Licensure requirements of niche products may vary. Examples of niche products may include vaccines for pet fish or public aquariums.

4. *Companion animals.* For studies where each enrolled animal is released to an individual owner after the immediate post-vaccination period, the owners may be given responsibility for certain follow-up observations, provided that:

a. Each owner is provided with a standardized reporting form and instructions for providing feedback (including the absence of adverse events). The investigator should follow up with owners who do not return the reporting form.

b. If the vaccination regimen includes multiple vaccine doses, a qualified investigator should thoroughly evaluate each animal when the animal is presented for each revaccination.

c. If an owner observes an adverse event, he/she should contact the qualified investigator for further guidance. Investigators are encouraged to schedule a follow-up examination of the animal(s) involved in an attempt to describe the adverse event more thoroughly and assess its relationship to the product.

E. Adverse Events

1. *Definition.* An adverse event (AE) is any observation in an animal that is unfavorable and unintended and occurs after the use of a veterinary product or investigational veterinary product, *whether or not test operators consider it product related.*[1]

1 The definition of AE for field safety studies is found in VS Memorandum No. 800.301 (II. Glossary 1.1).

2. *Types.* AEs may be local or systemic. Test operators should categorize AEs according to standardized low-level terms developed by the Veterinary Dictionary for Drug Regulatory Activities (VeDDRA).[2] The test operators may supplement VeDDRA terms with additional terms to specify further or clarify the AE. See section IV.F.5 for more information.

3. When AEs occur, the test operators should observe the animal until they can assess the duration of the event. Test operators may treat animals experiencing adverse events causing distress to the animal. Test operators should also record the magnitude or severity of the event. Cases of injection site reactions or lymphadenopathy may warrant histopathological evaluation so test operators can define the nature of the reaction.

F. Reporting Requirements

1. *Report All AEs.* Test operators should report all AEs, regardless of the individual making the observation. If a firm wishes to conclude that an event is not related to vaccination, a follow-up evaluation and diagnosis by a veterinarian or trained specialist should be included in the study report. Although it is not always possible to determine a definitive cause for an AE, test operators should attempt to provide objective evidence (e.g., laboratory results) to support the diagnosis.

2. *Necropsy.* Test operators should perform a necropsy on all test animals that die, and the findings must be included in the study report. For poultry and aquatic species, test operators may instead submit daily mortality sheets and slaughter condemnation reports, or the site veterinarian's assessment, although necropsy or diagnostic reports may be necessary to provide additional data regarding unusually high morbidity/mortality. Clearly traumatic deaths, such as hit by a car, do not require necropsies.

3. *Include All Animals.* The disposition of all animals enrolled in the study, including those that do not complete the study and for which follow-up data are unavailable, must be included in the final report.

4. *Presentation of Findings.* Applicants may describe the findings may be described with simple summary statistics set in the relevant context. Trials of this type are usually unsuitable for inferential statistical methods that depend on certain design elements.

5. *Data submission*. To facilitate rapid processing, applicants should submit data as indicated in the CVB Data Guide on the NCAH Portal Guidance web page.

[2] Combined VeDDRA list of terms, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/07/WC50009480 2.pdf