



Animal and Plant
Health Inspection
Service

Veterinary Services

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Washington, DC
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VETERINARY SERVICES MEMORANDUM NO. 800.50

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

FROM: Jack A. Shere
Deputy Administrator

SUBJECT: Basic License Requirements and Guidelines for Submitting Materials in Support of Licensure

I. PURPOSE

This memorandum provides guidance regarding the requirements for obtaining a U.S. Veterinary Biologics Establishment License, per title 9, *Code of Federal Regulations* (9 CFR), section 102.3(a), and a U.S. Veterinary Biological Product License, per 9 CFR 102.3(b). This memorandum specifies the information and documents an applicant must provide to APHIS in order for APHIS to complete licensing actions.

In addition, this memorandum lists additional regulatory resource documents available at the Center for Veterinary Biologics (CVB) Web site at https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_regs_guidance. The CVB encourages applicants to contact CVB's Policy, Evaluation, and Licensing (CVB-PEL) personnel in order to facilitate submission and review of materials.

Although many of the procedures for approving imported products match those required for domestically produced products, an applicant for a U.S. Veterinary Biological Product Permit (for imported products) should refer to [Veterinary Services \(VS\) Memorandum 800.101](#) for additional guidance.

II. CANCELLATION

This memorandum replaces VS Memorandum 800.50, dated February 9, 2011.

III. BACKGROUND

Veterinary biologics producers in the United States must have both a U.S. Veterinary Biologics Establishment License for their facility and a U.S. Veterinary Biological Product License for each product produced in their facility. To qualify for an establishment license, an applicant also must qualify for at least one product license. If an applicant, whether a company or individual, plans to market imported veterinary biological products in the United States, the CVB requires the applicant to have a U.S. Veterinary Biological Product Permit (Permit for Distribution and Sale).

IV. GUIDELINES FOR SUBMISSIONS

This section describes the materials an applicant must submit for the CVB to consider issuing establishment and product licenses. The address for submitting paper documents is:

Center for Veterinary Biologics-Policy, Evaluation, and Licensing
1920 Dayton Avenue
Ames, IA 50010

Although the CVB has a portal for Web-based submissions, an applicant must make initial submissions on paper. [Portal eligibility requirements for new establishments](#) are available on the NCAH [Portal Guidance page of the CVB website](#).

The CVB receives, reviews, and files an applicant's materials and notifies the applicant in writing regarding the acceptability of the submitted materials. If applicable, the CVB-PEL provides written comments on any revisions that an applicant must make and/or additional data that an applicant must submit.

A. Application for an Establishment License

1. An applicant must submit:

- a. Application for U.S. Veterinary Biologics Establishment License ([APHIS Form 2001](#)).
- b. Articles of incorporation for the applicant and any subsidiaries, if applicable (9 CFR 102.3).
- c. Water quality statement (9 CFR 108.11). Local water authorities must verify in a written statement that the facility is in compliance with effluent waste regulations.
- d. Application for at least one U.S. Veterinary Biological Product License ([APHIS Form 2003](#)) and applicable supporting documents described in section IV.B. below.
- e. Qualifications of Veterinary Biologics Personnel, ([APHIS Form 2007](#)) for key employees (9 CFR 114.7(a)). Licensed establishments must be operated under competent supervisors and employees (9 CFR 102.4). See [VS Memorandum 800.63](#) for additional guidance on preparing and submitting [APHIS Form 2007](#).
- f. Facility documents, include blueprints, plot plans, and legends (9 CFR 108.2–108.5). Refer to VS Memorandum 800.78 for guidance in preparing facility documents. An applicant must submit two copies of each document. The

CVB's Inspection and Compliance unit (CVB-IC) reviews and responds to the facility document submission.

2. CVB Actions

- a. The CVB-IC inspects the buildings, equipment, personnel and processes to determine if an applicant can consistently manufacture the product in compliance with the regulations and approved Outlines of Production. Although the CVB-IC performs the facility inspection, the CVB-PEL initiates the request for inspection. [Veterinary Services Memorandum 800.91](#) provides guidance for specific inspection categories. If the CVB-PEL has reviewed the establishment license application and supporting documents and an applicant has made satisfactory progress toward licensure of at least one product in accordance with the approved Outline of Production, the CVB-PEL initiates the request for inspection, which occurs before it issues the establishment license/permit.
- b. The CVB issues an establishment license only when the CVB qualifies a product for licensure that will be made in that establishment.

B. Application for a Product License

1. An applicant must submit:

- a. Application for U.S. Veterinary Biological Product License ([APHIS Form 2003](#)).
- b. Outline of Production (9 CFR 114.8–114.9) and, if applicable, Special Outlines (9 CFR 114.9(b)). See [VS Memorandum 800.206](#) for additional guidance regarding preparing and submitting Outlines of Production for select product types. Submission procedures described in this memorandum are applicable to other biological products that are not currently detailed in VS Memorandum 800.206.
- c. Master Seed and Cell Reports. For each microorganism (Master Seed) and cell stock (Master Cell) used in the production of biological products, an applicant must submit a report describing testing performed to evaluate the purity, identity, and safety of the seed and cell. An applicant must describe the source from which the seed or cell was obtained and all known passage history. [VS Memorandum 800.109](#) and the following regulations provide further guidance:

9 CFR 113.27(c & d)	Detection of extraneous viable bacteria and fungi in Master Seed Virus and Master Seed Bacteria
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VETERINARY SERVICES MEMORANDUM NO. 800.50

Page 4

9 CFR 113.51	Requirements for primary cells used for production of biologics
9 CFR 113.52	Requirements for cell lines used for production of biologics
9 CFR 113.55	Detection of extraneous agents in Master Seed Virus
9 CFR 113.64	General requirements for live bacterial vaccines
9 CFR 113.100	General requirements for inactivated bacterial products
VS Memo 800.113	Production, Testing and Storage of Master Seed and Cell Stocks at Alternate Locations
9 CFR 113.200	General requirements for killed virus vaccines
9 CFR 113.300	General requirements for live virus vaccines

The 9 CFR Standard Requirements for individual product types provide additional organism-specific requirements for Master Seeds. An applicant should refer to 9 CFR 113 to determine if a Standard Requirement exists for a particular product.

- d. Summary Information Formats (SIFs). If an applicant plans to use a Master Seed to produce new live biological products or produce a Master Seed using recombinant DNA technology, the CVB requires additional safety and identity data. An applicant must provide this information in a SIF.

The SIF is an “expandable document,” which is updated as an applicant generates applicable data to support the license application. The CVB requires a completed SIF before issuing a license. The initial version of the SIF, which an applicant should submit concurrently with the Master Seed report described in section IV.B.1.c, must provide data that are adequate for the CVB laboratory to establish proper biocontainment requirements and conduct confirmatory testing. See [VS Memorandum 800.205](#) for additional guidance and https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_sifs for document templates.

- e. Protocols for studies of host animal immunogenicity/efficacy, safety, backpassage, shed/spread, immunological interference, and other applicable areas. The CVB strongly recommends that applicants have the CVB review their protocol before performing a study. If an applicant would like to have the CVB comment on the proposed protocol, an applicant should submit the protocol at least 60 days before the proposed initiation date. The CVB provides additional guidance on study design in the following documents:

Diagnostic Test Kits	VS Memorandum 800.73
Potency Test Validation	VS Memorandum 800.112
Inactivation Kinetics	VS Memorandum 800.117
Study Practices and Documentation	VS Memorandum 800.200
Backpassage	VS Memorandum 800.201
Efficacy	VS Memorandum 800.202
Component Compatibility	VS Memorandum 800.203
Field Safety	VS Memorandum 800.204
Target Animal Safety	VS Memorandum 800.207

2. CVB Actions

a. Outline of Production or Special Outline

- (1) If the CVB determines that an applicant included objectionable features in the Outline of Production or that the Outline needs critical or extensive changes, the CVB may return the Outline unprocessed. An applicant must submit a revised Outline of Production that the CVB determines to be accurate and sufficient before licensure.
- (2) If the CVB determines that the Outline is satisfactory or requires only minimal changes, then the CVB processes the Outline by placing a CVB stamp in the lower right corner of each page. The CVB reviewer may make corrections to the Outline, which immediately become a part of the approved document, and/or may provide comments regarding changes the applicant must make before product licensure.

b. Master Seed or Master Cell Reports

- (1) If the CVB-PEL determines that the reports are satisfactory and complete, the CVB-PEL authorizes the facility to submit samples of Master Seed(s) and Master Cell Stock(s) to the CVB laboratory for confirmatory testing. Applicants should use an [APHIS Form 2070](#) to request permission to submit Seed and Cell samples for testing.
- (2) If the CVB determines that the CVB laboratory confirmatory testing of the Master Seed is satisfactory, then the CVB-PEL authorizes the applicant to produce serials (numbered lots) of product in production facilities.

C. Supporting Data for a Product License Application

1. An applicant must submit, as applicable to the product under consideration, the following additional reports and materials:
 - a. In-process procedures and corresponding validation reports:

- (1) Inactivation procedures for killed products.
 - (2) Maximum allowable moisture levels for desiccated products.
 - (3) Other Outline procedures, as appropriate.
- b. Host animal immunogenicity/efficacy reports:
- (1) Preliminary dose determination studies, if performed.
 - (2) Master Seed immunogenicity/efficacy studies. The regulations at 9 CFR 113 describe standard immunogenicity tests for certain organisms. An applicant must prepare the serial of product used to demonstrate efficacy at the highest allowable passage of the Master Seed being evaluated.
 - (3) Duration of immunity studies.
 - (4) Efficacy studies in maternal antibody-positive animals.
 - (5) Component compatibility studies.
 - (6) Any other studies needed to support specific product label indications and recommendations.
- c. Potency test development report. The regulations at 9 CFR 113.8 provide additional guidance on developing in vitro potency tests, as does VS Memorandum 800.112. If the protocol for the potency test is not codified in the CFR and the applicant does not use CVB reagents and procedures, the applicant must include in the report, as applicable:
- (1) Validation of the dose responsiveness, sensitivity, specificity, and reproducibility of the test.
 - (2) Data showing how the test correlates with (i.e., is sufficiently predictive of) host animal protection.
 - (3) Qualification data for all reference preparations.
 - (4) Procedures for monitoring the stability of, and requalifying, the reference preparation(s).
- d. Product safety reports:
- (1) Studies in laboratory animals.

- (2) Studies in host animals under biocontainment, including overdose studies.
 - (3) Data establishing the safety of any new, or significantly different, antigen-adjuvant formulation or additive. An applicant must establish a slaughter withholding period for products used in domestic animals if there is an edible portion of the animal which may be used for food purposes (9 CFR 112.2(8)). This includes products intended for use in horses, with the exception of foals. VS Memorandum 800.51 provides guidance for establishing slaughter withholding periods.
 - (4) Backpassage studies and shed/spread studies for modified live products.
 - (5) Field safety studies. See VS Memorandum 800.204.
- e. Stability reports from accelerated or preliminary real-time studies. See VS Memorandum 800.300 for specific stability requirements for products containing well-characterized proteins, polypeptides, and their derivatives.
 - f. Veterinary Biologics Production and Test Reports (APHIS Form 2008) for three consecutively prepared serials (identified as prelicensing serials) that are prepared and tested in accordance with the approved Outline of Production. See VS Memorandum 800.53 for guidance on completing APHIS Form 2008.

Each new antigen (i.e., one that has not been previously approved as part of a licensed product) must be prepared from a separate antigen production lot for each of the prelicense serials. Single lots of previously approved antigens may be combined with the new antigen(s). An applicant may use one lot of production seed to prepare each prelicense serial; however, an applicant must use separate vials of production seed for each lot of antigen an applicant prepares. Definitions for seeds are found in 9 CFR 101.7. The minimum volume of each serial should approximately equal one-third of an average serial, as defined in the Outline of Production.

- g. Labels and/or label sketches prepared according to 9 CFR 112 and VS Memorandum 800.54. An applicant must provide acceptable scientific data to support all label claims.

2. CVB Actions

- a. Reports. The CVB-PEL reviews supporting data and provides official responses to each submission.

- b. APHIS Form 2008 for prelicense serials. If the CVB determines that test results from the prelicense serials are satisfactory and an applicant prepared the serials in the same manner as the serial(s) demonstrating efficacy and safety, the CVB-PEL authorizes the applicant to submit product samples to the CVB laboratory for confirmatory testing. Applicants should use [APHIS Form 2072](#) to request permission to submit prelicense serial samples. An applicant must select and submit representative product samples to the laboratory according to the procedures described in 9 CFR 113.3. An applicant must include [APHIS Form 2020](#) (Shipment and Receipt of Biological Samples) with all shipments.
- c. The CVB-IC determines the eligibility for marketing release of the prelicense serials and subsequent serials. See [VS Memorandum 800.53](#).
- d. Labels and/or Label Sketches.
 - (1) Finished labels or computer-generated label proofs that have an appearance identical to the proposed final label:
 - (a) If the CVB-PEL determines that the labels are satisfactory, the CVB-PEL retains the labels until it issues the product license. Approved labels are returned to the applicant at the time of licensure. An applicant must have an approved final product label at the time of licensure.
 - (b) If the CVB-PEL determines that the labels are unsatisfactory, the CVB-PEL processes the labels as sketches and provides comments so the applicant can revise them.
 - (2) Labels submitted to the CVB-PEL as sketches (appearance may or may not be identical to that of the proposed finished label): sketches are labels which may or may not have an identical appearance to the proposed finished label. The CVB-PEL processes such labels as sketches, with or without comments, at the time of review.

D. Requests to Conduct Field Studies

An applicant must receive CVB-PEL approval prior to shipping unlicensed (experimental) veterinary biological products. The regulations at 9 CFR 103.3 describe the shipment of product for field safety or field efficacy studies. Applicants should use [APHIS Form 2071](#) as a cover for such submissions.

VETERINARY SERVICES MEMORANDUM NO. 800.50

Page 9

1. When requesting to ship experimental product for such studies, an applicant must include the following:
 - a. Permit or letter of authorization from proper State or foreign animal health authorities for each State or country where the study will be conducted.
 - b. Tentative list (names and addresses) of proposed recipients and study cooperators. An applicant must include the lot identification (serial number) and quantity of experimental product to be shipped to each individual.
 - c. Description of the experimental product, including recommendations for use and the results of preliminary safety and efficacy studies (if not previously submitted). An applicant must specifically address the safety of the product in meat-producing animals, if applicable, and describe the product according to the appropriate Outline of Production guidelines in 9 CFR 114.9.
 - d. Test results of experimental serials. Before an applicant uses an experimental serial in field studies, an applicant must complete all serial release tests defined in section V of the Outline of Production. At a minimum, an applicant must test the serials for purity, completeness of inactivation (if applicable), and safety in animals. The CVB may require an applicant to perform additional testing.
 - e. Labels for the experimental product. An applicant must submit a label containing the statement “Notice! For experimental use only—not for sale” or its equivalent. An applicant must not place the U.S. Veterinary License Number (establishment number) on the label. An applicant should not submit an APHIS Form 2015 with the experimental product labels and should provide two copies if submitting on paper. See [VS Memorandum 800.67](#) for additional guidance.
 - f. Study protocol. See [VS Memorandum 800.200](#).
 - g. Statement from the research investigator or research sponsor agreeing to provide additional information concerning each group of meat animals involved before moving these animals from the premises where the test is to be conducted, when applicable.
 - h. Environmental release risk assessment. This assessment, to comply with National Environmental Protection Act (NEPA) regulations, applies to products not exempted by categorical exclusion in 7 CFR 372.5(c). In general, this requirement applies to conventionally derived modified live products and those derived by recombinant DNA technology. An applicant

must submit the information in the SIF described for environmental releases. The CVB uses the SIF when evaluating the safety of the product in the context of the target environment.

2. CVB Actions

- a. Products exempted from environmental risk assessment. If the CVB determines that the protocol and supporting documents are satisfactory, the CVB-PEL authorizes an applicant to ship the experimental product for field studies. The CVB-PEL returns a date-stamped copy of the experimental label to the applicant. Authorization is effective for not more than one year from the date it is given. An applicant must submit a summary of the results of each study to the CVB-PEL or notify the CVB-PEL if an applicant has not performed a study.
- b. Products requiring an environmental release risk analysis. The CVB-PEL reviews all risk assessments according to the guidelines outlined in "[Risk Analysis for Veterinary Biologics](#)" and by NEPA.
 - (1) If the CVB determines that the risk assessment supports a Finding of No Significant Impact (FONSI), then APHIS publishes the risk assessment (purged of confidential business information) in the *Federal Register* for comment. At the end of the comment period and after APHIS has satisfactorily addressed the public comments, APHIS may authorize field studies.
 - (2) If the CVB determines that the risk assessment indicates that the product may have a significant affect on the environment, APHIS prepares an Environmental Impact Statement, and the field study must meet additional APHIS and NEPA guidelines.
 - (3) At the conclusion of the field study, the CVB-PEL confirms that the study findings support the FONSI of the environmental assessment.

V. EXEMPTION FROM FREEDOM OF INFORMATION ACT

VS considers all submissions confidential, subject to the [APHIS Policy Statement on the Protection of Privileged or Confidential Business Information](#) (APHIS Notice 85-406). If an applicant considers a submission to be exempt from the Freedom of Information Act (5 U.S.C. 552), the applicant should include a statement in the submission describing the specific adverse effects the applicant would experience if any portion of the submission were disclosed. [VS Memorandum 800.66 contains](#) guidance on identifying confidential information in submissions.

VETERINARY SERVICES MEMORANDUM NO. 800.50

Page 11

VI. APHIS FORMS

Forms listed in this memorandum are available on the biological forms Web site, https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms. Alternatively, the CVB-PEL provides forms if contacted at the address in section IV above.