VETERINARY SERVICES MEMORANDUM NO. 800.50

TO: VS Management Team (VSMT)
    Directors, Center for Veterinary Biologics
    Biologics Licensees, Permittees, and Applicants

FROM: John R. Clifford     /s/ Mark E. Teachman, for
      Deputy Administrator

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

I. PURPOSE

This memorandum gives guidance on 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 APHIS needs to complete licensing actions.

It also lists additional regulatory documents for specific items that are available at the Center for Veterinary Biologics (CVB) Web site at www.aphis.usda.gov/animal_health/vet_biologics/vb_regs_and_guidance.shtml. Applicants are encouraged to interact with CVB’s Policy, Evaluation, and Licensing (PEL) personnel to facilitate submission and review of materials.

Although many of the procedures for approval of imported products are identical to those required for domestically produced products, persons wishing to apply 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 May 28, 2002.

III. BACKGROUND

Producers of veterinary biologics in the United States must have a U.S. Veterinary Biologics Establishment License and a U.S. Veterinary Biological Product License for each product. To qualify for an establishment license, an applicant also must qualify for

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at least one product license. For those companies or individuals wishing to market imported veterinary biological products in the United States, a U.S. Veterinary Biological Product Permit (Permit for Distribution and Sale) is required.

IV. GUIDELINES FOR SUBMISSIONS

This section describes the items applicants must submit to CVB before CVB can issue establishment and product licenses. The address for submitting documents is:

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

CVB actions taken upon receipt and review of specific submissions are also described. In general, CVB-PEL will review and file the submitted materials. It will provide the firm official notification, in writing, regarding the acceptability of submitted materials. If applicable, CVB-PEL will provide comments on revisions that must be made or additional data that must be submitted.

A. Application for an establishment license

1. Applicants must submit:


   b. Articles of incorporation for the applicant and any subsidiaries, if applicable (9 CFR 102.3).

   c. Water quality statement (9 CFR 108.11). This statement from local water authorities must verify that the facility is in compliance with regulations for effluent waste.

   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 supervision and by competent employees (9 CFR 102.4). See VS Memorandum 800.63 for additional guidance on preparing and submitting APHIS Form 2007.
f. Facility blueprints, plot plans, and legends (9 CFR 108.2–108.5). Refer to VS Memorandum 800.78 for guidance in preparing facility documents. Submit two copies of each document.

2. CVB actions:

a. After CVB-PEL has reviewed the establishment license application and supporting documents and the applicant has made satisfactory progress toward licensure of at least one product, CVB’s Inspection and Compliance will inspect the facilities before licensure.

b. CVB issues an establishment license only after a product to be made in that establishment has qualified for licensure.

B. Application for a product license

1. Applicants must submit:


b. Outline of Production (9 CFR 114.8–114.9) and, if applicable, Special Outlines (9 CFR 114.9(b)). Submit two copies of each outline, each containing original signatures. Submit each outline with APHIS Form 2015 (Transmittal of Labels and Circulars or Outlines). An acceptable outline must be on file with CVB before licensure. See VS Memorandum 800.206 for additional guidance regarding preparation of Outlines of Production for vaccines, bacterins, antigens, and toxoids.

c. Master Seed and Cell Reports. For each microorganism (Master Seed) and cell stock (Master Cell) used in the production of biological products, submit a report that describes testing performed to evaluate the purity (freedom from extraneous agents), identity, and safety of the seed and cell. Describe the source from which the seed or cell was obtained and all known passage history. See VS Memorandum 800.109 for guidance. Refer to the following regulations for further guidance:
<table>
<thead>
<tr>
<th>Regulation</th>
<th>Description</th>
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<tbody>
<tr>
<td>9 CFR 113.27(c &amp; d)</td>
<td>Detection of extraneous viable bacteria and fungi in Master Seed Virus and Master Seed Bacteria</td>
</tr>
<tr>
<td>9 CFR 113.51</td>
<td>Requirements for primary cells used for production of biologics</td>
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<tr>
<td>9 CFR 113.52</td>
<td>Requirements for cell lines used for production of biologics</td>
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<tr>
<td>9 CFR 113.55</td>
<td>Detection of extraneous agents in Master Seed Virus</td>
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<tr>
<td>9 CFR 113.64</td>
<td>General requirements for live bacterial vaccines</td>
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<tr>
<td>9 CFR 113.100</td>
<td>General requirements for inactivated bacterial products</td>
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<tr>
<td>9 CFR 113.200</td>
<td>General requirements for killed virus vaccines</td>
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<tr>
<td>9 CFR 113.300</td>
<td>General requirements for live virus vaccines</td>
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Additional organism-specific requirements for Master Seeds are found in the 9 CFR Standard Requirements for individual product types. Refer to 9 CFR 113 to determine if a Standard Requirement exists for a particular product.

d. Summary Information Formats (SIFs). For Master Seeds to be used in the production of new live biological products and for all Master Seeds produced by recombinant DNA technology, additional safety and identity data are required. This information is provided in a SIF.

The SIF is an “expandable document,” which is updated as applicable data are generated to support the license application. A completed SIF is required before licensure. The initial version of the SIF, submitted concurrently with the Master Seed report described in Section IV.B.1.c, must contain data that are adequate for the CVB laboratory to establish proper biocontainment requirements and to conduct confirmatory testing. See VS Memorandum 800.205 for additional guidance. Document templates are available at www.aphis.usda.gov/animal_health/vet_biologics/vb_sifs.shtml.

Submit two copies.

e. Protocols for studies of host animal immunogenicity/efficacy, safety, backpassage, shed/spread, immunological interference, and other applicable areas. Submit two copies of a protocol at least 60 days before the proposed initiation date of the study if you wish to have the CVB
provide comments on the proposed protocol (highly recommended). The following documents contain additional guidance on study design:

- Diagnostic Test Kits
- Study Practices and Documentation
- Backpassage
- Efficacy
- Component Compatibility
- Field Safety

2. CVB actions:

a. Outline of Production or Special Outline:

(1) If critical or extensive changes are needed, CVB may return the outline unprocessed for revision, noting its comments on APHIS Form 2015. A revised, acceptable outline must be submitted before licensure.

(2) If the outline is satisfactory or requires only minimal change, CVB processes the outline by placing a CVB stamp in the lower right corner of each page and files it pending licensure. The reviewer may make pen-and-ink corrections to the outline. A detailed listing of changes, as well as any additional comments about the outline, is noted on the APHIS Form 2015. One copy is returned to the applicant.

b. Master Seed or Master Cell Reports:

(1) If the reports are satisfactory and complete, CVB-PEL will authorize the submission of samples of Master Seed(s) and Master Cell Stock(s) to the CVB laboratory for confirmatory testing.

(2) CVB-PEL will authorize the applicant to produce serials of product in production facilities after the CVB laboratory completes satisfactory confirmatory testing of the Master Seed.

C. Supporting data for a product license application

1. Applicants must submit, as applicable to the product under consideration, two copies of 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. Standard immunogenicity tests for certain organisms are described in 9 CFR part 113. The serial (numbered lot) of product used to demonstrate efficacy must be prepared 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) Immunological interference studies.

(6) Any other studies needed to support specific product label indications and recommendations.

c. Potency test development report. (For additional guidance on the development of in vitro potency tests, see 9 CFR 113.8 and VS Memorandums 800.90 and 800.112.) Unless the protocol for the potency test is codified in the 9 CFR and CVB reagents and procedures are used, the report must include, 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 to establish the safety of any new, or significantly different, antigen-adjuvant formulation or additive. This includes the establishment of a slaughter withholding period for products used in domestic animals, the edible portion of which may be used for food purposes (9 CFR 112.2(8)). This includes products intended for use in horses (but not foals). Guidance for establishing slaughter withholding periods is available in VS Memorandum 800.51.

(4) Backpassage studies and shed/spread studies for modified live products.

(5) Field safety studies.

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 satisfactory prelicensing serials (numbered lots) of product (three consecutive serials). See VS Memorandum 800.53 for guidance on completing APHIS Form 2008.

Prepare each new antigen (i.e., one that has not been approved as part of a previously licensed product) in the prelicense serials from separate batches of ingredients (e.g., medium, cells, and stabilizer) according to the filed Outline of Production. A single lot of a previously approved antigen may be combined with the antigen(s) not previously licensed. Seed from one production seed lot may be used to prepare each prelicense serial, if at least one separate container of production seed is used as inoculum for each serial. (See 9 CFR 101.7 for seed definitions.) The minimum volume of each serial should be approximately equal to one-third that of an average serial as defined in the Outline of Production.

g. Labels and/or label sketches, prepared according to 9 CFR part 112 and VS Memorandum 800.54. All label claims must be supported by
acceptable scientific data. See VS Memorandum 800.202 for a description of acceptable label claims. Submit two copies of each finished label and each sketch with an APHIS Form 2015.

2. CVB actions:

a. Reports. CVB-PEL will review supporting data and provide official responses to each submission by hard-copy mail.

b. APHIS Form 2008 for prelicense serials. If test results from the prelicense serials are satisfactory, and the serials were prepared in the same manner as the serial(s) with which efficacy and safety were demonstrated, CVB-PEL will authorize the firm to submit product samples to the CVB laboratory for confirmatory testing. The firm must select and submit product samples to the laboratory according to the procedures described in 9 CFR 113.3. All shipments must be accompanied by APHIS Form 2020 (Shipment and Receipt of Biological Samples).

c. 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 satisfactory, CVB-PEL will retain the labels with the product file until the license is issued. Approved labels will be returned to the applicant at the time of licensure. Products must have an approved final label at the time of licensure.

   (b) If unsatisfactory, CVB-PEL will process the labels as sketches and provide comments to facilitate revisions.

(2) Labels submitted to CVB-PEL as sketches (appearance may or may not be identical to that of the proposed finished label). CVB-PEL will process such labels as sketches, with or without comments, at the time of review.

D. Requests to conduct field studies

Shipment of unlicensed (experimental) veterinary biological products requires prior approval from CVB-PEL. Shipment of product for field safety or field efficacy studies is regulated under 9 CFR 103.3.
1. When requesting to ship experimental product for such studies, applicants must include the following:

   a. Permit or letter of authorization from proper State or foreign animal health authorities for each State or country in which the study is to be conducted.

   b. Tentative list (names and addresses) of proposed recipients and study cooperators. 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). Specifically address the safety of the product in meat-producing animals, if applicable. Describe the product according to the appropriate Outline of Production guidelines in 9 CFR 114.9.

   d. Test results on experimental serials. Before using an experimental serial in field studies, complete all serial release tests defined in Section V of the Outline of Production. At a minimum, test the serials for purity, completeness of inactivation (if applicable), and safety in animals. CVB may require additional testing.

   e. Labels (two copies) for the experimental product. This label must contain the statement, “Notice! For experimental use only—not for sale,” or its equivalent. The U.S. Veterinary License Number (establishment number) must not appear on the label. Do not submit an APHIS Form 2015 with experimental product labels. See VS Memorandum 800.54 for additional guidance.

   f. Study protocol.

   g. Statement from the research investigator or research sponsor agreeing to provide additional information concerning each group of meat animals involved, before movement of these animals from the premises where the test is to be conducted, when applicable.

   h. Environmental release risk assessment. This assessment, to comply with the regulations of the National Environmental Protection Act (NEPA), 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. Submit the information in the SIF described for environmental
releases. This SIF evaluates the safety of the product in the context of the target environment.

2. CVB actions:

a. Products exempted from environmental risk assessment. If the protocol and supporting documents are satisfactory, CVB-PEL will authorize shipment of the experimental product for field studies. CVB-PEL will return a date-stamped copy of the experimental label to the applicant. Authorization is effective for not more than 1 year from the date it is given. Applicants must submit to CVB-PEL a summary of the results of each study or notify CVB-PEL if a study is not performed.

b. Products requiring an environmental release risk analysis. CVB-PEL will review all risk assessments according to the guidelines set forth in “Risk Analysis for Veterinary Biologics” and by NEPA.

1) If the risk assessment supports a Finding of No Significant Impact (FONSI), then the risk assessment (purged of confidential business information) is published in the Federal Register for comment. At the end of the comment period and after satisfactorily addressing the public comments, APHIS may authorize field studies.

2) If the risk assessment indicates that the product may have a significant effect 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, CVB-PEL confirms that the findings of the study support the FONSI of the environmental assessment.

V. EXEMPTION FROM FREEDOM OF INFORMATION ACT

All submissions are considered to be confidential, subject to the APHIS Policy Statement on the Protection of Privileged or Confidential Business Information (APHIS Notice 85-406). If the applicant considers a submission to be exempt from the provision of 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.
VI. APHIS FORMS

Forms listed in this memorandum are available at www.aphis.usda.gov/animal_health/vet_biologics/vb_forms.shtml. Alternatively, you can contact the CVB-PEL for forms at the address given in Section IV above.