May 28, 2002

VETERINARY SERVICES MEMORANDUM NO. 800.50

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

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

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) 102.3(a), and a U.S. Veterinary Biological Product License, per 9 CFR 102.3(b). This memorandum specifies the information and documents needed by APHIS to complete applicable licensing actions and lists additional sources of information for specific items. Note that the regulatory documents cited in this document are available at the CVB website at www.aphis.usda.gov/vs/cvb/regsandguidance.htm. Applicants are also encouraged to interact with Center for Veterinary Biologics-Licensing and Policy Development (CVB-LPD) personnel, as necessary, 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 Permit (for imported products) should refer to Veterinary Services (VS) Memorandum No. 800.101 for additional specific guidance.

II. CANCELLATION

This memorandum cancels VS Memorandum No. 800.50, dated September 7, 1999, and VS Memorandum No. 800.84, dated July 23, 1999.

III. BACKGROUND

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

The following sections describe the items that must be submitted to the CVB before an establishment and/or product license can be issued. Submit materials to CVB-LPD, at the address listed below, unless otherwise indicated.

Center for Veterinary Biologics-Licensing and Policy Development
510 S. 17th Street, Suite 104
Ames, IA 50010

Submitted materials will be reviewed by CVB-LPD and filed. Official notification regarding the acceptability of submitted materials will be provided to the firm in writing. If applicable, CVB-LPD will provide comments regarding revisions that must be made or additional data that must be submitted. Additional CVB actions taken upon receipt and review of specific submissions are also described at the end of each of the following sections.

A. Application for Establishment License

1. *Applicants 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). 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 Part 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 No. 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 Memo No. 800.78 for guidance in preparing facility documents. The CVB currently requires submission of two copies of each document.

2. *CVB Actions:*

a. CVB-IC will inspect the facilities prior to licensure, after CVB-LPD has reviewed the establishment license application and supporting documents and the applicant has made satisfactory progress toward licensure of at least one product.

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:*

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)) Submit four copies of each Outline, two of which contain original signatures. Each Outline submission must be accompanied by APHIS Form 2015 (Transmittal of Labels and Circulars or Outlines).

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/cell. Describe the source from which the seed/cell was obtained and all known passage history. Refer to the following regulations for further guidance:

9 CFR 113.27(c & d)	Detection of extraneous viable bacteria and fungi in Master Seed Virus and Master Seed Bacteria
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
9 CFR 113.200	General requirements for killed virus vaccines
9 CFR 113.300	General requirements for live virus vaccines

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 Center for Veterinary Biologics-Laboratory to establish proper biocontainment requirements and to conduct confirmatory testing. The SIFs for the following types of products are available at www.aphis.usda.gov/vs/cvb/LPD/sifs.htm. Submit three copies.

1. Category I Recombinant Veterinary Biologics
2. Category II Recombinant Veterinary Biologics
3. Category III Recombinant Veterinary Biologics
4. Conventionally Derived, Modified Live Veterinary Biologics

(Note: Additional information about CVB risk assessment procedures is found in “Risk Analysis for Veterinary Biologics” available from APHIS, CVB-LPD.)

e. Protocols for studies of host animal immunogenicity/efficacy, safety, backpassage, shed/spread, immunological interference, and other applicable areas. Submit three copies of each protocol. Submit a protocol at least 60 days prior to 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:

Study Practices and Documentation	VS Memorandum No. 800.200
Backpassage	VS Memorandum No. 800.201
Efficacy	VS Memorandum No. 800.202
Interference	VS Memorandum No. 800.203
Field Safety	VS Memorandum No. 800.204
Diagnostic Test Kits	VS Memorandum No. 800.73

2. *CVB Actions:*

a. Outline of Production or Special Outline:

(1) If critical and/or extensive changes are needed, the Outline may be returned unprocessed for revision. All copies of the Outline, except one for the CVB files, are returned to the applicant. Comments regarding the Outline are noted on APHIS Form 2015. A revised, acceptable Outline must be submitted prior to licensure.

(2) If the Outline is satisfactory or requires only minimal change, the Outline is processed (CVB stamp is placed in lower right-hand corner of each page) and filed pending licensure. One copy is returned to the applicant. 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, are noted on the APHIS Form 2015.

b. Master Seed or Master Cell Reports:

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

(2) CVB-LPD will authorize the applicant to produce serials of product in production facilities after confirmatory testing has been satisfactorily completed at the CVB-L.

C. Supporting Data for a Product License Application

1. *As applicable to the product under consideration, applicants must submit the following additional reports and materials to support a product license application.* Submit three copies of each item, unless otherwise indicated.

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 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, when applicable

(4) Efficacy studies in maternal antibody-positive animals, when applicable

(5) Immunological interference studies, when applicable

(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 Memorandum No. 800.90.) Unless the protocol for the potency test is codified in the 9 CFR and CVB-L 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 demonstrating how the test correlates with (i.e., is sufficiently predictive of) host animal protection.

(3) Qualification data for all reference preparations. See VS Memorandum No. 800.90 for further guidance on references for *in vitro* assays.

(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 and/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 No. 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 No. 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 No. 800.53 for guidance on completing APHIS Form 2008.

Each new antigen (i.e., one that has not been approved as part of a previously licensed product) in the prelicense serials must be prepared from separate batches of ingredients (e.g., medium, cells, stabilizer) according to the filed Outline of Production. Applicants may combine a single lot of a previously approved antigen with the antigen(s) not previously licensed. Applicants may use seed from one production seed lot to prepare each prelicense serial, provided that 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 112 and VS Memorandum No. 800.54. All label claims must be supported by acceptable scientific data. See VS Memorandum No. 800.202 for a description of acceptable label claims. All label submissions must be accompanied by APHIS Form 2015. Submit two copies of each finished label and each sketch.

2. *CVB Actions:*

a. Residue clearance report: If an unapproved antigen-adjuvant or additive formulation is being used, or if a reduced clearance period prior to slaughter for a previously approved formulation is requested, CVB-LPD will forward the report to the Food Safety Inspection Service (USDA-FSIS) for consultation. CVB-LPD will coordinate inspection of animals at slaughter, if needed. Note that separate residue clearance approvals must be obtained for each food animal species in which the formulation is to be used.

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-LPD will authorize the firm to submit product samples to the CVB-L for confirmatory testing.

Product samples must be selected and shipped to the CVB-L 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-LPD 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-LPD will process the labels as sketches. Comments will be provided to facilitate revisions.

(2) Labels submitted to CVB-LPD as sketches (appearance may or may not be identical to that of the proposed finished label): CVB-LPD 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-LPD. Shipment of product for field safety or field efficacy studies is regulated under 9 CFR 103.3.

1. *Requests to ship experimental products for such studies 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). The safety of the product in meat-producing animals, if applicable, specifically must be addressed.

d. Labels (2 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. Experimental product labels should not be submitted with APHIS Form 2015. See VS Memorandum No. 800.54 for additional guidance.

e. Study protocol

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

g. 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 by 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, available

on the CVB website at www.aphis.usda.gov/vs/cvb/LPD/sifs/vber.html, 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-LPD will authorize shipment of the experimental product for field studies. A date-stamped copy of the experimental label will be returned to th applicant. Authorization is effective for not more than one year from the date it is given. Applicants must submit to CVB-LPD a summary of the results of each study or notify CVB-LPD if a study is not performed.

b. Products requiring an environmental release risk analysis: CVB-LPD 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(s) supports a Finding of No Significant Impact (FONSI), then the risk assessment(s) (purged of confidential business information) is published in the Federal Register for comment. At the end of the comment period, and after all public comments have been satisfactorily addressed, field studies may be authorized.

(2) If the risk assessment indicates that the product may have a significant effect on the environment, an Environmental Impact Statement must be prepared, and additional APHIS and NEPA guidelines must be followed.

(3) At the conclusion of the field study, CVB-LPD 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 USC 552), that submission should include, or be accompanied by, a statement describing the specific adverse effects they would experience if any portion of the submission was disclosed.

VI. APHIS FORMS

This memorandum is generally distributed as part of a licensing package that contains copies of each of the APHIS forms listed in this memorandum. If you did not receive a licensing package, or if you need additional copies of any of these forms, requests may be made to CVB-LPD at the address given in Part IV above. Selected forms are also available at www.aphis.usda.gov/vs/cvb.

/s/ W. Ron DeHaven

W. Ron DeHaven
Deputy Administrator
Veterinary Services