# New Firm Informational Packet for Antivenin Products

## Background Information

The purpose of this packet is to give an overview of the licensing process to new firms unfamiliar with the process of licensing a biologic. The information should be viewed only as an introduction and not a list of all possible requirements. Each product will have unique characteristics that may require its own unique studies to assure the final licensed product is safe and effective.

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 must qualify for at least one Product License. The Establishment and Product Licenses are issued simultaneously.

The Center for Veterinary Biologics (CVB) consists of two operational units: Policy, Evaluation, and Licensing (PEL) and Inspection and Compliance (IC). These units closely interact during the prelicensing stage of new products as well as after licensing. The PEL unit is responsible for licensing of new products and maintenance of products once licensed. Licensing of new products consists of review of Outlines of Production, review of study protocols and associated reports/data, laboratory testing, and issuing Establishment and Product licenses. The IC unit is responsible for inspections of new facilities (including review of blueprints, plot plans, and legends), product marketing release, initiating investigations when appropriate, conducting periodic firm inspections, responding to issues related to product performance, and implementing our pharmacovigilance program.

The following is a brief outline of submissions to submit to the CVB to support licensure. Links to relevant guidance documents are provided. While this example is for a new, unlicensed vaccine/bacterin, the general theme holds true for most products.

Please be aware that CVB relies on formal, signed paper copy documents to be submitted by your firm. Email, meetings, and phone conversations are considered informal and non-binding communication. CVB will formally respond with our decisions and recommendations concerning licensure by paper copy. There is a specific process for communicating with CVB which also contains an introduction to the licensing process described in *Veterinary Service Memorandum (VSM) 800.50: Basic License requirements and guidelines for submitting materials in support of licensure*:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

A complete set of biologics-related guidelines, memorandums, notices, and related forms are available online at the *Veterinary Biologics* website:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics

*APHIS Forms 2001, 2003, 2005, 2007, 2008, 2015, 2070, 2071, and 2072* are located at the site below:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms

The *Submission Compliance Guide: Submitting Complete and Accurate Paper License Applications, Outlines, and Labels* provides step wise directions on making these submissions.

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_regs_guidance

The CVB website describes the thorough and extensive licensing process in detail. One informal resource that helps bring together the overlapping guidance documents is the *CVB Policy, Evaluation and Licensing - Reviewer Manual* and is available on the CVB website at:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_pelmanual_toc

There are also several organizations outside of the USDA that may be used to assist in the licensing process. Two professional organizations, Animal Health Institute (AHI) and Association of Veterinary Biologics Companies (AVBC), have members from biologics firms and consultants which may be able to assist new firms through the licensure process. Additionally, the Institute for International Cooperation in Animal Biologics (IICAB) in cooperation with the CVB provides week-long training annually on U.S. veterinary biologics licensing requirements.

**The following list is general guidance for antivenin products and should not be considered an all-inclusive list. Formal communication between your firm and your CVB Reviewer will determine the appropriate licensing pathway for your unique product. However, it is the firm's obligation to understand and meet all the licensing requirements.**

**I. The initial submission to the CVB is an introduction of your company and product. The goal is to determine if your product falls within CVB regulatory jurisdiction. The submission should include**:

- A cover letter with the following information:
  - Brief description of the product including mechanism of action
  - Animal species for which the product is intended
  - Proposed label claim (what you propose the product will do)
  - Names and addresses of all legal entities (not individual persons) involved in the manufacture of the product
  - Supporting publications for antivenin products should provide rationale and data on why the product would be expected to be efficacious. This may take the form of human data if the proposed veterinary product is manufactured by the same manufacturer for human treatment of envenomation. Supporting information

justifying claims for cross-protection against venom from heterologous species should also be provided.

- If it is determined your product falls under CVB jurisdiction an individual Reviewer will be assigned to your firm. See the *Memorandum of Understanding between the APHIS and the FDA* for additional details on jurisdiction:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_regs_guidance

## II. Core documents required prior to any study submissions

- *APHIS Form 2001 Application for United States Veterinary Biologics Establishment License*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms

  - Articles of Incorporation

  The following documents associated with the APHIS Form 2001 may be submitted at a later date:

  - Water Quality Statement verifying the effluent waste for the facility meets local regulatory standards
  - Facility documents; see *VSM 800.78 Preparation and Submission of Facilities Document*s:

    https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo800-78.pdf

- *APHIS Form 2003 Application for United States Veterinary Biological Product License or APHIS Form 2005 Application for United States Veterinary Biological Permit*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms

- For imported antivenin products, an APHIS Form 2005 for "General Sale and Distribution," is used in place of the APHIS Forms 2001 and 2003. This is because the product will be "permitted" and not "licensed."
  See more detailed information in *9 CFR 104 PERMITS FOR BIOLOGICAL PRODUCTS* and *9 CFR 104.5 Products for distribution and sale:*

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_cfr

  https://www.aphis.usda.gov/library/forms/pdf/APHIS2005.pdf

  It is important to realize that a separate "Research and Evaluation" permit which also uses the APHIS Form 2005 is required to bring an imported product into the U.S. for evaluation.

Information on how to obtain an importation permit is found at *9CFR 104.4 Products for research and evaluation:*

*https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_cfr*

An importation SIF is required at the time the "Research and Evaluation" permit is considered for issuance to bring the imported product into the U.S. This information is found in: *Summary Information Format for the Importation of Veterinary Biological Products into the United States:*

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_sifs

- *APHIS Form 2007 Qualifications of Veterinary Biologics Personnel*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms

  Identify persons who will act as Liaison and Alternate Liaison(s), which should be reflected on APHIS Form 2007. This is the person who will represent your company to CVB on all correspondence, see *VSM 800.63 Personnel at Licensed Establishments*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

- An Outline of Production submitted with *APHIS Form 2015 Transmittal of Labeling or Outlines*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms

  This key document describes how you make your product. See *Veterinary Services Memorandum (VSM) 800.206 General Licensing Considerations: Preparing Outlines of Production for Vaccines, Bacterins, Antigens, and Toxoids and Diagnostic Test Kits*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

  *9 CFR 114.8: Outline of Production required*, *9 CFR 114.9 (c): Outline of Production guidelines and CVB Notice 19-03*

Note: Because most antivenin products are manufactured in horses, donor horses must be shown to be free of specific equine foreign animal diseases (i.e., piroplasmosis, dourine, glanders, equine infectious anemia, brucellosis, and equine parvovirus).

The Outline of Production should describe the source from which the immunizing microorganism or venom(s) were obtained, acceptance criteria of purchased venom(s) and testing performed to confirm that the purity, identity, and safety of the venom(s) are required. For example, each venom should be tested by SDS-PAGE or other approved methods to ensure the identity of each venom.

https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=4b71249719aef16788f85e60ab1873fe&mc=true&tpl=/ecfrbrowse/Title09/9CIsubchapE.tpl

Reviewer manual *Chapter 4 Outlines of Production and Special Outlines*:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_pelmanual_toc

*VSM 800.51 Additives in Administered Animal Biological Products*:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

**III. The following are the core scientific submissions and their associated guidance documents. Many of the pivotal studies required below typically begin with the submission of a protocol as described in *VSM 800.200 General Licensing Considerations: Study Practices and Documentation* following *VSM 800.301 Good Clinical Practices*. Most of the final reports for these studies will need to be accompanied by properly formatted electronic data (CVB Data Guide).**

https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_200.pdf

https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_301.pdf

https://www.aphis.usda.gov/animal_health/vet_biologics/publications/16-CVBDataGuide.pdf

- Efficacy and safety are evaluated in clinical studies with client-owned animals that have been envenomated in the field and have natural disease. These field target animal efficacy and safety studies are required to support the label claim(s). Efficacy is generally evaluated using the Snakebite Severity Score (SSS). Study protocols should be submitted for review prior to conducting these studies. Client consent forms must accompany the protocol. The study design

will primarily follow the requirements of *VSM 800.202 General Licensing Consideration: Efficacy Studies*:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

Reviewer Manual *Chapter 4 Efficacy Studies*:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_pelmanual_toc

Safety will also be evaluated in these combined field efficacy and safety studies. Aspects of VSM 800.204 should be incorporated into the combined safety and efficacy study. See VSM 800.204 *General Licensing Considerations: Field Safety Studies*:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

Reviewer Manual *Chapter 4 Field Safety Studies*:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_pelmanual_toc

- Target Animal Safety for vaccines in a laboratory setting. Protocols are generally reviewed in advance for these studies. See *VSM 800.207 General Licensing Considerations: Target Animal Safety (TAS) Studies Prior to Product Licensure – VICH Guideline 44*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

- Purity and potency, serial release testing and test method validation.

  Purity tests are based on
  *9 CFR 113.26 Detection of viable bacteria and fungi except in live vaccine:*

  https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=4b71249719aef16788f85e60ab1873fe&mc=true&tpl=/ecfrbrowse/Title09/9CIsubchapE.tpl

  Generally, potency testing of antivenin serials consist of a venom neutralization mouse study to determine the median protective dose and a Western Blot using the antisera to identify a known set of bands in each venom to which antibodies are generated against. The venom-neutralization assay involves vaccinating mice with a preparation consisting of a constant concentration of

venom incubated with varying antivenin dilutions. At least 80% of mice must survive the vaccination. A Western Blot provides confirmation that the antibodies in the antivenin recognize the known banding pattern for each venom.

- Product Stability studies are required postlicensure.
  *9 CFR 114.13 Determination of the dating period of a product*:

  https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=4b71249719aef16788f85e60ab1873fe&mc=true&tpl=/ecfrbrowse/Title09/9CIsubchapE.tpl

## IV. Shipment of your experimental biologic

Because the unlicensed product is considered to be experimental in nature, authorization to ship the product for conduct of efficacy, safety, or other studies must be authorized by the CVB. Guidance for shipment of product for these studies is under *9 CFR 103.3. Shipment of Experimental Biological Products.*

https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=4b71249719aef16788f85e60ab1873fe&mc=true&tpl=/ecfrbrowse/Title09/9CIsubchapE.tpl

See *VSM 800.67 Shipment of Experimental Biological Products:*

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

Additional guidance regarding shipment of experimental product may be found at:

Reviewer Manual *Chapter 6 Shipping Experimental Product:*

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_pelmanual_toc

An *APHIS Form 2071 Application for Authorization to Ship Experimental Veterinary Biological Products* may be used to request authorization to ship experimental product and may be accessed at:

https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms

Note: if the product is a recombinant product, an evaluation of your SIF is required well before any movement of the product outside of containment would be allowed.

## V. Prelicense serial testing

- CVB will require confirmatory testing of your three prelicense serials.
  *VSM 800.50: Basic License requirements and guidelines for submitting materials in support of licensure*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

  *APHIS 2072 Application for Authorization to Ship Biological Product Samples for Confirmatory Testing by APHIS*

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/sa_bio_forms/ct_vb_forms

## VI. Prelicense facility inspection

- Guidance regarding the CVB-IC prelicensing inspections process which is initiated by your reviewer is at:

  Inspection and Compliance Manual *Chapter 3 Process for Prelicense Inspection Requests*

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_icmanual_toc

  *VSM 800.91 Categories of Inspection for Licensed Veterinary Biologics Establishments* describes important categories evaluated during the inspection process:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

  General guidance on the authority for inspections and record keeping requirements are found in *9 CFR 115 Inspections* and *9 CFR 116 Records and Reports*

  *https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_cfr*

  Note: a prelicensing inspection must be completed by CVB-IC prior to issuance of an establishment license or permit. If the product is being imported, the quarantine facility must also be inspected by CVB-IC prior to issuance of a permit. If it has been longer than two years since the prelicensing inspection, a second prelicensing inspection will most likely need to be completed prior to issuance of the establishment license or permit.

## VII. Becoming Portal Enabled

- The NCAH Portal is a valuable communication tool for both the firm and CVB. However, the CVB receives numerous inquiries from new establishments each year, with only a subset of those proceeding beyond the initial inquiry, so initial communication is via paper letters and not via the electronic Portal. Access to submit submissions via the *NCAH Portal Guidance for CVB Submitters* may be considered for prelicense firms, as described below:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_regs_guidance

## VIII. Final submissions prior to licensure

- Final labeling materials guidance:

  See *9 CFR 112 Packaging and labeling*:
  https://www.ecfr.gov/cgi-bin/text-idx?gp=&SID=4b71249719aef16788f85e60ab1873fe&mc=true&tpl=/ecfrbrowse/Title09/9CIsubchapE.tpl

  See *VSM 800.54 Guidelines for the Preparation and Review of Labeling Materials*:

  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_vs_memos

  Reviewer Manual *Chapter 4 Labels:*
  https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/veterinary-biologics/biologics-regulations-and-guidance/ct_vb_pelmanual_toc

  See information on advertising that is not part of labeling in *VSM 800.95 Advertising and Promotional Materials*

  https://www.aphis.usda.gov/animal_health/vet_biologics/publications/memo_800_98.pdf