

New Firm Informational Packet for Cancer Products and Immunomodulatory Products that Require Client Owned Animals Efficacy and Safety Studies

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 live and killed vaccines 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

- 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 Documents:*

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

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

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

- *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 and 9 CFR 114.9: Outline of Production guidelines:

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

III. Combined safety and efficacy pilot studies in client owned animals

Cancer products and other immunomodulator products often require the treatment of client owned animals with naturally occurring disease to identify preliminary evidence of efficacy early in the licensing process. The firm must provide preliminary evidence that the product is scientifically sound, at low risk to the environment, at low risk to the user, and have preliminary safety data directly from the target species. This analysis is needed before you would be allowed to ship your experimental biologic product per 9 CFR 103.3 for pilot studies in client owned animals.

These preliminary studies designed to protect client owned animals are typically smaller in scale than normal regulatory studies and thus will not meet the full regulatory requirements necessary for conditional or full licensure listed below.

In general, all the items discussed in Sections I and II of this document will need to be completed before CVB will consider approving any pilot studies in client owned animals.

The central document describing both preliminary studies and pivotal studies necessary for immunotherapeutics is found in *Veterinary Services Memorandum (VSM) 800.126 Efficacy and Safety Studies for Cancer Immunotherapeutics*:

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

- IV. **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

- Master Seed, Master Cell, and Master Sequence Reports describing the source from which the seed or cell was obtained and all known passage history, testing performed to evaluate the purity, identity, and safety of the seed and cell are required. Protocols are generally not reviewed in advance for these studies. Each Master Seed, Master Cell, and Master Sequence is unique and may require additional testing.

VSM 800.109 Master Seed and Master Cell Stock Testing Report Submission:

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

9 CFR 113.27 (c & d): Detection of extraneous viable bacteria and fungi in live vaccines (Master Seeds)

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

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

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

Reviewer Manual *Chapter 4 Master Seeds/Cells/Sequences*:

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

CVB will conduct confirmatory testing on all Master Seed, Master Cell, and Master Sequences. Please use *APHIS Form 2070 Application for Authorization to Ship Master Seed or Cell Samples for Confirmatory Testing by APHIS* to request permission to submit samples for confirmatory testing:

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

- There are additional key requirements for conventionally-derived live products and all biotechnology- derived products to evaluate environmental safety.

Summary Information Format (SIF): A SIF is required for all live Master Seeds used to produce new live conventionally-derived biological products or the Master Seeds that are biotechnology-derived using methods such as recombinant technology. The SIF is a dynamic document that is updated as the applicant generates applicable data from the studies below to support licensure. If your product is live or biotechnology-derived, the preliminary SIF will be required very early in the licensing process. The preliminary SIF should be submitted prior to the Master Seed report and is used to establish proper biocontainment requirements for CVB confirmatory testing. Submission of a final SIF with all information except field safety results must occur before any studies outside of containment are allowed and could take 6-12 months if a notice in the Federal Registry is required to comply with the National Environmental Policy Act.

VSM 800.205 General Licensing Considerations: Biotechnology-derived Veterinary Biologics Categories I, II, and III:

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

Additional clarification of the requirements for the *Risk Analysis/Summary Information Formats* is located at:

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

- Backpassage/Shed-Spread Studies for live products containing conventional modified live or live recombinant vaccines. This examines the possibility of the vaccine to shed into the environment, spread to adjacent animals, or reversion to virulence after five passages in the target species. Tissue tropism should also be examined. Protocols are generally reviewed in advance for these studies. See *VSM 800.201 General Licensing Considerations: Backpassage Studies*:

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

- Shed and spread studies in non-target species, tissue tropism, as well as environmental release and persistence studies may also be required. Protocols are generally reviewed in advance for these studies. See *Risk Analysis/Summary Information Formats*:

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

Additional requirements unique to killed products. Inactivation kinetic data for killed products to ensure complete inactivation. See *VSM 800.117 Guidance for Inactivation Studies*:

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

- Target animal efficacy studies are required for each fraction of each product. Duration of immunity studies will be required for some products. Protocols are generally reviewed in advance for these studies. See *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

- Immunological (component) interference. Protocols are generally reviewed in advance for these studies. See *VSM 800.203 General Licensing Considerations: Compatibility of Components*:

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

- 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

- Field Safety Studies to evaluate the safety of final product in a large number of representative animals in normal field conditions. Protocols are generally reviewed in advance for these studies 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

- Adjuvant studies are required for adjuvanted products and protocols are generally reviewed in advance for these studies. See *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

Reviewer Manual *Chapter 4 Adjuvants and Excipients*:

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

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

Purity tests are based on *9 CFR 113.25 Culture media for detection of bacteria and fungi*, *9 CFR 113.26 Detection of viable bacteria and fungi except in live vaccine*, and *9 CFR 113.27 Detection of extraneous viable bacteria and fungi in live vaccines*:

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

Many potency tests have standardized requirements in various sections of 9 CFR 113. For individual potency test development, protocols are generally reviewed in advance for the study. The *9 CFR 113.8 In vitro tests for serial release* and *VSM 800.112 Guidelines for Validation of In Vitro Potency Assays* provide guidance on developing in-vitro potency tests. These studies will validate the various potency and testing methods within your OP:

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

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

For products whose potency assay contains a reference, a reference stability monitoring protocol is required to describe how the stability of the reference material will be monitored over time after licensure. See *VSM 800.112 Guidelines for Validation of In Vitro Potency Assays*.

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

Reviewer Manual *Chapter 4 Potency Test Development & Validation Studies*:

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

- Product Stability studies are required post-licensure.
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/Title09/9CIsu_bchapE.tpl

V. **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/Title09/9CIsu_bchapE.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.

VI. 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

VII. 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 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.

VIII. 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

IX. 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/Title09/9CIsu_bchapE.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

- Efficacy/Safety Individual Study Summaries (ISS) and the Product Compilation Summary are required for vaccines, bacterins, toxoids, and immunomodulators. Products exempted from the Single Tier Rule and the Single Tier Summary Study requirements are antibody products, diagnostic test kits, autogenous or prescription products, and allergenic extracts. Detailed information is found in *Single Tier Label Claim Industry Guidance*.

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