Animal and Plant Health Inspection Service

Veterinary Services

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Establishment Licenses

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Notes:

Establishments and Permittees

Mention of trademark or proprietary product does not constitute a guarantee or warranty of the product by USDA and does not imply its approval to the exclusion of other products that may be suitable.

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1. Purpose and Scope

This chapter focuses on the initial, administratively-oriented steps involved in proceeding to licensure or permitting, and briefly, to related steps occurring just before licensure or permitting. Biologics manufacturers located in the United States are called *licensees*. Licensees must have an establishment license that is separate from their product licenses. The establishment license is evidence that the Center for Veterinary Biologics (CVB) considers the facilities, and personnel operating them, to be adequate to produce consistent, quality biologics.

U.S. companies (or individuals) that import biological products made in foreign countries so that they can be distributed and sold in the United States are called *permittees*. They are not "licensed"; they obtain a Biological Product Permit for Sale and Distribution for each product. Each permit combines aspects of establishment and product approvals.

2. Establishment and Permit Codes

Licensees and permittees are issued establishment and permittee codes (numbers), respectively. [redacted]

A single company can serve both as a licensee and a permittee if it produces biologics domestically as well as importing foreign-made products. In such cases, the same base number is used.

Example: [redacted]

Separate permits are issued for each imported product. If a permittee imports products from several different foreign manufacturers, a different alphabetic suffix is used to differentiate the permits issued to the same applicant, to denote different foreign manufacturers.

Example: [redacted]

Requesting a code assignment (Establishment, Permit, or Product): Codes should be assigned upon receipt of the application (APHIS Form 2001, 2003, or 2005) and the first submission to which the reviewer can respond (generally the Outline of Production). Do not assign codes to companies or individuals merely inquiring about licensing procedures or requesting guidance about the regulatory jurisdiction of their proposed product. Prompt code assignment is important so that submissions can be tracked and filed efficiently.

[redacted]

[redacted]

Once the Establishment No. and the first Product Code and True Name (and abbreviated True Name, if applicable) have been assigned, that information should be provided to the firm. This could be done in an initial letter, or could be included in the reviewer's response to a different submission, such as the Outline or firm's license plan. New firms should also be told to request approval of a USDA Liaison (by submission of an APHIS Form 2007), and it may be helpful to direct them to the CVB web site for applicable documents located there, such as the guidance for new firms located at USDA APHIS | Suggestions for New Biologics Applicants. [redacted]

3. Reviewing Establishment License Applications

Regulations regarding biologics establishments are found in title 9, *Code of Federal Regulations* (9 CFR), sections 102.4 and 108. The following are required to support an establishment license application:

3.1 The APHIS Form 2001

[redacted] When appropriate, supporting legal documentation should be requested.

Specified Information, by Block on the Form 2001:

3.1.1 Name and address of applicant (Block 4): This should include the complete name (no acronyms) and the *legal* address. The address should include a street address (or some other descriptor of the physical location of the premises), not just a post office box number. If the application is submitted because of a name or ownership change, ensure the appropriate legal paperwork (in addition to the APHIS Form 2001 and letter from the firm) is included to support the change. In the case of an establishment ownership change only (no name change), legal documents other than the application (APHIS Form 2001) and the firm's letter are required to show official transfer of the company, but reissuance of the current license is not necessary if the contents remain the same.

3.1.2 Address for official mail from the CVB (Block 5): Although this is usually the same as the legal address and/or one of the licensed premises, firms may elect to have mail delivered to an alternate address. Firms with multiple premises must designate a single address for all CVB correspondence.

3.1.3 Proof of incorporation (Block 12): If the applicant is a corporation, they must submit their Articles of Incorporation. The applicant name in Block 4 should agree with the name on the Articles of Incorporation.

In some corporate structures, the name of the applicant is separate from the name of the parent company. In such cases, both the applicant name and the parent company should be listed on the APHIS Form 2001.

3.1.4 Subsidiaries (Block 7): Applicants may elect to declare subsidiaries on their establishment license application. Subsidiaries are special designations because a subsidiary name can be used *in lieu of* the licensee's name on product labels.

The CVB has a strict legal definition for a subsidiary (9 CFR 101.2): a subsidiary is a *corporation* in which the *corporate* licensee owns *in excess of* 50 percent of the voting stock. [redacted]

3.1.5 Divisions (Block 8): The codified definition (9 CFR 101.2) for a division is a marketing unit established by the licensee which may be named on labels, advertisements and promotional material *in addition to* the name and address of the producer (licensee).

3.1.6 Licensed premises (Block 9): This section should include all of the locations where regulated activities take place. In most cases, the legal address is also one of the licensed premises, but exceptions exist (e.g., if the legal address only contains corporate office space). Each of the licensed premises appears on

the Establishment License, as locations where the licensee is "hereby licensed to maintain…an establishment for the preparation of biological products…"

Each entry in Block 9 should include a street address. Rural Route numbers may not be used. The street address may be a Locatable Address Conversion System address (a "911" address). If no other specific method is available, a description relative to the nearest named intersecting roads may be used.

CVB-Inspection and Compliance (CVB-IC) inspects each of the licensed premises. Inspections are conducted by the Biologics Specialist ("inspector"). Ensure that the list of licensed premises is complete and accurate by conferring with the Specialist who performed the prelicense inspection of the establishment or the inspection of new premises that are being added to the license.

3.1.7 Signature/date (Blocks 17-19): The application must have an *original,* dated signature or valid digital signature. The firm's USDA Liaison (other appropriate person, if the Liaison is not yet designated) should sign the form.

3.2 Blueprints/legends/plot plans of the facilities

CVB-IC reviews and approves facility documents. New applicants sometimes submit them to CVB-PEL [redacted]

The location of third party testing facilities, when applicable, must be disclosed prior to CVB approval. Facility documents of the third party site must be submitted, as well as a letter from the third party clearly allowing CVB-IC to inspect the facilities. If the site is acceptable, it will be added to the establishment license. **The CVB does not consider inclusion of a location on the establishment license to imply ownership**, but to identify the sites that are officially acceptable for preparation, storage, and distribution of veterinary biologics. In certain instances, potency and safety testing may be conducted in unlicensed facilities, in accordance with Veterinary Services Memorandum 800.115; these facilities are not listed on the Establishment license.

3.3 Water quality statement

Regulations (9 CFR 108.11) specify that applicants must file a document verifying that the *effluent waste* (not incoming water) for the facility meets local regulatory standards. Some municipalities (or rural areas) do not have any regulations regarding effluent waste. In such cases, the applicant should submit a letter from the appropriate local authority stating that the area has no regulations in this regard.

3.4 Satisfactory prelicense inspection

Each of the premises that appear on the establishment license must be inspected by CVB-IC prior to licensure and must be found satisfactory for the purpose for which it will be used. [redacted] If years pass between the prelicense inspection and licensure, it may be necessary for CVB-IC to perform a follow-up inspection to ensure that the facility remains adequate.

Reviewers should submit requests for prelicense inspections using the "Make Request" function in the MailLog. Unlike inspections after licensure (generally unannounced), prelicense inspections are usually announced. Details regarding requesting a "special inspection" are provided in [redacted] A "special inspection" may also occur post-licensure, in response to an event or finding.

The Specialist should update the reviewer following the facility inspection. Before recommending an establishment for licensure, reviewers should confirm with the specialist leading the prelicense inspection to verify that the inspection was satisfactory and the applicant is ready for licensure. This also applies to situations where an establishment requests a new establishment license to add new premises.

3.5 Personnel documents (the APHIS Form 2007)

Part of the requirements for an establishment license is provision of evidence that the personnel operating the facility are competent by education and experience to consistently produce a quality product under the Outline of Production. Individuals with key responsibilities within the establishment must file an APHIS Form 2007; see Veterinary Services Memorandum 800.63 for additional details.

The establishment must designate a Liaison to interact with the CVB. Alternate Liaisons also may be designated. Even though the establishment proposes the liaison and alternates, it is the responsibility of the reviewer to determine whether the designation is appropriate and to accept the proposals. A Liaison must be designated and approved prior to issuance of the establishment license or permit, and must be US resident. The firm may also designate one or more Alternate Liaisons. This is generally done by the recognized Liaison, and the request is accompanied by a Form 2007. The CVB discourages the use of too many Alternate Liaisons.

Each licensed establishment must have one government liaison representing all premises listed on the establishment license. This liaison is responsible for and should handle all government submissions and correspondence and will coordinate inspection activities

and compliance. The licensee should designate a Site Contact that is approved by the CVB to coordinate compliance and unannounced inspections at locations beyond a reasonable travel time from the normal location of the liaison. See Veterinary Services Memorandum 800.87 for additional information.

CVB-IC directly receives, reviews, and files most Forms 2007. Requests for proposed Liaisons (and Alternate Liaisons) should be submitted to IC and then looped to the reviewer. Once the reviewer has accepted (or rejected) the proposed Liaison, the child loop is closed and CVB-IC is responsible for database entry and filing. If more than one reviewer are responsible for the firm, include an em: notification to each reviewer.

4. Reviewing Permittee Information on applications for a permit for Sale and Distribution

Regulations regarding permits for distribution and sale are covered in 9 CFR 104.5. See also VSM 800.101. Many of the establishment requirements for licensees, described earlier in this chapter, also apply to permittees. The following are differences:

4.1 A permittee must be a U.S. resident. Foreign companies often wish to market their products directly in the United States, but this is not allowed. The permittee, who must reside within the United States, takes legal responsibility for the product once it enters the country. [redacted]

Some foreign manufacturers will contact the CVB directly at first, promising to identify a permittee shortly. **Reviewers should ensure that a valid applicant exists before spending too much time reviewing submissions. Critical submissions should be submitted by the permittee, not the foreign manufacturer, so that the permittee takes legal responsibility for the submissions.**

4.2 CVB-IC must inspect the permittee's domestic facilities, called a "quarantine site," where product is stored and held until released by the CVB for sale, AND the foreign manufacturing site. The permittee must agree to periodic re-inspection by CVB-IC of both the foreign manufacturing facility and the quarantine site. The foreign manufacturer or the permittee must agree to pay expenses for the inspection, as stated on the permit restriction. [redacted]

4.3 The APHIS Form 2005 is used to apply for a Permit for Sale and Distribution. The 2005 is used for three types of CVB permits, but the one most relevant to reviewers is the permit for General Sale and Distribution. The other types are permits for research and evaluation, and permits for transit shipment through the United States. These are issued by the Office of the Assistant Director, CVB, Ames. IA.

Portal users should follow the NCAH Portal User Guide 29 and enter the information electronically. Non-portal users must fill out the hard copy APHIS Form 2005.

As with the APHIS Form 2001, the LIE should check the portal entry or the Form 2005 prior to routing the submission to the reviewer. The reviewer should carefully examine the application form and verify all items. Note: Only some of the data blocks on the application are applicable to permits for Sale and Distribution. See the list below for clarification regarding some items:

4.3.1 The name and address of the applicant (Block 3 on paper submissions): This should specify the full name of the permittee and the permittee's legal address in the United States (not just a P.O. box number). Although there is no designated space for a separate mailing address on the permit application, permittees are allowed to designate an alternate mailing address within the United States (such as a P.O. box). The mailing address is specified on the issued permit. Additional information not fitting on the Form 2005 may be attached to it.

4.3.2 The name and address of the producer (Block 4 on paper submissions): This should contain the name and address of the foreign manufacturer.

4.3.3 The address of the storage facilities (Block 11 on paper submissions): A permittee must have an adequate facility to receive and store imported product (adequate "quarantine site"). Each serial of the product must be held there until it is released by CVB-IC for distribution and sale in the United States.

4.3.4 An applicant for a permit for distribution and sale must specify a U.S. port of entry (Block 8), and this information is listed on the permit. The applicant must designate which port it will routinely use. More than one port or the designation "multiple" is acceptable (on the Form 2005).

4.3.5 The type of organization (Blocks 12-13 on paper submissions): This pertains to the organizational structure of the **permittee**, not the foreign manufacturer.

4.3.6 Principal Officers or Partners (Block 14 on paper submissions): This pertains to the organization in the United States. Accountability is based on the Articles of Incorporation (which should be submitted with the Form 2005).

4.3.7 Signature of authorized official (Block 16 on paper submissions): This should be the signature of the permittee, not an official of the foreign manufacturer.

5. Preparing to License an Establishment or Issue a Permit – Final Steps pursuant to issuance.

5.1 Once the applicant has met all requirements for licensure or permitting, an establishment license is issued simultaneously with the first product license for the establishment (2 documents). A licensed establishment must have at least one valid product license at all times. The permit is issued as one document (the permit).

5.2 An establishment checklist is available in Section 8 of the Reviewer Manual (CVB-WI-0295) to ensure that all of the requirements for the establishment have been met. Enclose a completed checklist when the licensing or permitting package (all relevant submissions and responses, checklists, etc.) is sent forward for issuance. See Section 5.5 of this document.

5.3 Ensure that all necessary corrections to the establishment license or permit application have been made prior to sending the licensing or permitting package to the support staff for processing. This may require having the applicant submit a corrected copy of the application (Form 2001, 2003, or 2005) or a new portal submission (Form 2005) to supersede the information in the original submission.

5.4 [redacted]

5.5 See the Reviewer's Manual chapter titled, *Final Steps for Licensure* (CVB-SOP-0063) for additional details regarding procedures for preparing a license package and issuance. The CVB Director's signature is the final approval in issuing a license or permit for Distribution and Sale.

6. Miscellaneous "Establishments"

Reviewers often interact with companies/institutions that will never be licensees because they do not desire to produce and market biologics on a commercial scale. Examples include:

- Academic institutions
- Government research facilities
- Contract research or test companies
- "Think tank" research groups
- Diluent manufacturers

They are often involved in the transfer of technology to biologics manufacturers and thus are frequently in contact with the CVB regarding early submissions for product licensure and/or requests to ship experimental product.

[redacted]

[redacted]

[redacted]

Signature Manifest

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