

ESTABLISHMENTS and PERMITTEES

Overview

This chapter focuses on aspects of biologics establishments. 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 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 sold and distributed in the United States are called *permittees*. They are not “licensed”; they obtain a Biological Product Permit for Sale and Distribution. This single permit combines aspects of establishment and product approvals.

Establishment and Permit Codes

Licensees and permittees are issued establishment and permit 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, as per [CVB Notice 13-03](#). 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, for different foreign manufacturers.

Example: [REDACTED]

Requesting a code assignment: Codes should be assigned upon receipt of the first “real” submission. (Do not assign codes to companies or individuals merely inquiring about licensing procedures or requesting guidance about the regulatory jurisdiction of their

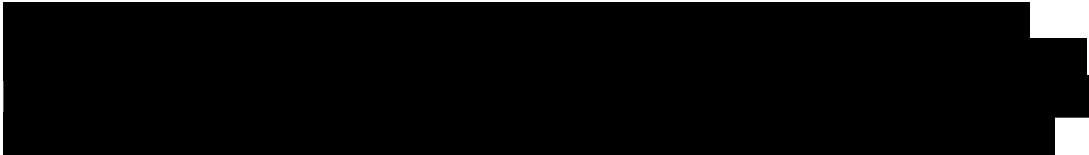
proposed product.) Prompt code assignment is important so that submissions can be tracked and filed efficiently.



Reviewing Establishment License Applications

Regulations regarding biologics establishments are found in 9CFR Sections 102.4 and 108. The following are required to support an establishment license application:

1. APHIS Form 2001



When appropriate, supporting legal documentation should be requested.

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 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 (2001) and firm 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.

1.2 Address for official mail from 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 (usually a P.O. box). Large firms with multiple premises must designate a single address for all CVB correspondence.

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.

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 (9CFR 101.2): a subsidiary is a *corporation* in which the *corporate* licensee owns *in excess of 50* percent of the voting stock. [REDACTED]

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).

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 addresses. Rural addresses should include a specific "911" address (instead of a general "Rural Route") if one has been assigned. If no 911 address exists, a description relative to the nearest named intersecting roads may be used.

CVB-IC inspects each of the licensed premises. Ensure that the list of licensed premises is complete and accurate by conferring with the IC specialist who performed the prelicense inspection of the establishment.

1.7 Signature/date (Blocks 17-19): The application must have an *original*, dated signature. The USDA liaison should sign the form.

2. Blueprints/legends/plot plans of the facilities

CVB-IC reviews and approves these facility documents. New applicants may submit them to CVB-PEL; [REDACTED]

Location of third party testing vendors, when applicable, must be disclosed prior to approval. Facility documents of the third party site must be submitted, as well as a permission letter from the third party vendor allowing CVB IC to inspect the facilities. If the site is deemed acceptable, it will be added to the establishment

license of the firm. CVB does not consider inclusion of a location on the establishment license to imply ownership, but rather to identify the sites that are officially acceptable for preparation and distribution of veterinary biologics.

3. Water quality statement

Regulations (9CFR 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.

4. Satisfactory prelicense inspection by CVB-IC

Each of the premises that appears 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 to the Section Leader for Inspections. Unlike inspections after licensure, prelicense inspections are not usually unannounced. Details regarding requesting a special inspection may be reviewed in

[REDACTED]

The IC 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.

5. Personnel documents (APHIS Form 2007)

Part of the requirements for an establishment license is providing evidence that the personnel operating the facility are competent by education and experience to produce a consistent quality product. 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.

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 will designate a site contact that is approved by the Center for Veterinary Biologics, (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 2007s. 2007s for proposed liaisons (and alternates) are an exception, as they should be submitted to the reviewer. Once the reviewer has accepted the proposed liaison(s), the 2007 and a copy of the approval letter should be forwarded to CVB-IC for database entry and filing. Send an em: to the Biologics Specialist for the firm and the BCA.

Reviewing Permittee Information on Permit Applications

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

1. A permittee must be a U.S. resident *or* operate a company within the U.S. Foreign companies often wish to market their products directly in the U.S., but this is not allowed. The permittee, who must be located within the U.S., 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 permittee 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.**

2. CVB-IC must inspect the permittee's domestic facilities (often only a quarantine site) AND the foreign manufacturer. The permittee must agree to periodic inspection by CVB-IC of both the foreign manufacturing facility and the domestic facility. The foreign manufacturer or the permittee must pay expenses for the inspection, as stated on the permit restriction. [REDACTED]

3. APHIS Form 2005 is used to apply for a veterinary biological product permit. There are only three types of permits, but the one most relevant to reviewers is the permit for

sale and distribution. (The other types are a) permits for research and evaluation, and b) permits for transit shipment through the United States. These are issued by the Section Leader, CVB-Operational Support, in Riverdale, Maryland.)

As with the APHIS Form 2001, the LIE should check APHIS Form 2005 prior to routing the submission to the reviewer. The reviewer should carefully examine the application form and verify all items prior to recommending issuance of the permit. Only some of the data blocks on the application are applicable to permits for sale and distribution.

3.1 Name and address of applicant (Block 3): This should contain the full name of the permittee and the permittee's legal address in the U.S. (not just a P.O. box number). Although there is no designated space for a separate mailing address on a permit application, permittees are allowed to designate an alternate mailing address within the U.S. (such as a P.O. box). The mailing address is specified on the issued permit.

3.2 Name and address of producer (Block 4): This should contain the name and address of the foreign manufacturer.

3.3 Address of storage facilities (Block 11): A permittee must have an adequate facility to receive and store imported product. Each serial of the product must be quarantined until it is released by CVB-IC for distribution in the U.S.

3.4 Even though the instructions for APHIS Form 2005 indicate that an applicant for a permit for sale and distribution does not need to specify a U.S. port of entry (Block 8), this information is listed on the actual permit. The applicant needs to designate which port it will routinely use. More than one port or the designation "multiple" is acceptable.

3.5 Type of organization (Blocks 12-13): This pertains to the organizational structure of the permittee, not the foreign manufacturer.

3.6 Principal Officers or Partners (Block 14): This pertains to the organization in the U.S. Accountability is based on the Articles of Incorporation.

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

Preparing to License an Establishment or Issue a Permit

1. An establishment license is issued simultaneously with the first product license for the establishment. A licensed establishment must have at least one valid product license at all times.

2. An establishment checklist is available in Section 8 of the reviewer manual on sharepoint at [REDACTED] to ensure that all of the requirements for an establishment license (or establishment considerations for a permit) have been met. Enclose a completed checklist when the licensing package is sent forward for signature.
3. Ensure that all necessary corrections to the establishment license or permit application have been made prior to sending the application to the support staff for processing. This may require having the applicant submit a corrected copy of the application.
4. [REDACTED]
[REDACTED]
[REDACTED] when the licensing package is sent forward for processing and signature.
5. See the chapter titled “Final Steps for Licensure” for additional details regarding the office procedure involved with preparing a license and obtaining the director’s signature.

Miscellaneous “Establishments”

Reviewers often interact with companies/institutions that will never be actual licensees because they do not have the capacity or 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

They are often involved in the transfer of technology to actual 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]