Animal and Plant Health Inspection Service

Veterinary Services

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Prelicensing Inspections for New Establishments/Products

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Notes: *An outcome of the BPI Prelicensing to Licensed Firms project*

Prelicensing Inspections for New Establishments/Products

Source Document: CVB-SOP-0035, The Inspection Proper

Prior to a prelicensing inspection request, the following documents must be submitted to CVB, also listed in CVB-WI-0093, Process for Prelicensing Inspection Requests (formerly ICWI0064):

1. APHIS Form 2001, 2003,or 2005
    a. Addresses of all manufacturing, testing, and storage sites should be entered in LSRTIS
    b. Sites should be marked as Pending
2. Reviewed Outline of Production (OP) with PEL comments
3. Facility Documents – preliminary review by Specialist against information listed in the filed OP
4. APHIS Form 2007
    a. Including Contact Information – especially important for foreign sites, including phone and email. Cannot prepare Cooperative Service Agreements without this information.
    b. Liaison must be assigned and entered into LSRTIS. Key site personnel may also entered in LSRTIS (especially for foreign sites, including phone and email)
5. Summary Information Format (SIF) for the Importation of Veterinary Biological Products into the United States (for permittees only)

Pre-Inspection Activities, also see CVB-SOP-0034 (formerly ICSOP0012)
This step is very important. We should be knowledgeable about their product and facilities. This is an opportunity to start a good working relationship with the firm.

1. Prelicensing inspections are announced. A mutually agreed upon time is set by the Specialist conducting the inspection and the firm's Liaison prior to scheduling the inspection in LSRTIS.
    a. Ensure the facilities are complete. If the facility is still under construction, do not perform the prelicensing inspection
    b. Ensure the equipment is installed and working as expected (validated)
    c. In most cases, at least a prototype serial has been prepared.

2. These inspections are usually conducted by one Specialist; usually a Senior Specialist, Section Leader or Director.

3. They are usually 3-4 days in length, depending on the number and complexity of the products being considered for licensure.

4. Review mail log (ML) items – can use Master Search or split search by IC or PEL
    a. Many times these firms are a result of a Veterinary Biologics Investigation (VBI), review the VBI as this inspection or licensure of the establishment/firm may close the VBI if not already closed
    b. There may be PEL MLs relevant to the inspection

5. Review the Licensing Plan(s) – LSRTIS

6. Review the Outline(s) of Production to familiarize yourself with the production and testing process.
    a. Read all comments made by the Reviewer regarding changes needed. Review associated ML items and talk to the Reviewer to see what progress had been made on the comments. Ask the Reviewer if the product is going to have restrictions. Ask the Reviewer if the product will serve as the initial licensed product that will establish subsequent production platform and/or prescription platform biologics.
    b. If you have questions about processes, ingredients or testing listed, discuss or email questions to the Reviewer. There should be a clear understanding of what is required.
    c. Areas of concern may be ingredients of animal origin and testing requirements under 9 CFR 113.53.

7. Review the Facility Documents submitted. Normally facility documents are not filed prior to the on-site inspection.
    a. Ensure the essential equipment needed for production and testing are listed in the facility documents, based on the review of the Outline of Production.
    b. See if you can determine the movement of product, materials, equipment and personnel and if it appears reasonable based on the review of the Outline of Production.

8. Fill out an APHIS Form 2008 and APHIS Form 2020 for the product being licensed. This is twofold, it provides a template for the firm and it can point out gaps in the Outline of Production, Section V (i.e., ensure validity requirements are listed for testing).

9. Print out applicable Veterinary Services Memoranda (VSM) and CVB Notices for the firm. While they have access to the CVB Website, they can use the hard copy to take notes as we review them during the inspection. These may include the following:
    a. VSM 800.53, Release of Biological Products
    b. VSM 800.59, Veterinary Biological Product Samples
    c. VSM 800.91, Categories of Inspection for Licensed Veterinary Biologics Establishments
        i. May also make a copy for you, as a type of inspection list of items to review
        ii. Review and highlight sections that are most applicable to the firm and product
    d. VSM 800.122, Recordkeeping and Compliance with 9 CFR Part 116

    AS NEEDED
    e. VSM 800.69, Guidelines for Autogenous Biologics
        NOTE, regulatory flexibilities regarding adjacent, non-adjacent herd use and extension of isolates not available to them until such time as we are confident in their processes to maintain compliance with 9 CFR 113.113
    f. VSM 800.73, Diagnostic Test Kit Validation
    g. VSM 800.101, U.S. Veterinary Biological Product Permits for Distribution and Sale – especially useful to describe what is required for serial release

h. VSM 800.206, General Licensing Considerations: Preparing Outlines of Production for Vaccines, Bacterins, Antigens, and Toxoids and Diagnostic Test Kits
i. VSM 800.57, Market Suspensions and Post Marketing Temperature Deviations
j. VSM 800.210, Manufacturing Deviations Identified Prior to Marketing Release
NOTE, regulatory flexibilities regarding process deviations are not available to them until such time as we are confident in their processes
k. VSM 800.213, Licensing Guidelines for Production Platform-Based, Non-Replicating, Nonviable Products
l. VSM 800.214, Prescription Platform Biologics

On-site Inspection Activities, also see CVB-SOP-0035 (formerly ICSOP0013) and VSM 800.91

There are two major outcomes from a prelicensing on-site inspection.

1. Determine if the facilities, equipment, personnel, and processes are appropriate for the production and testing as listed in the filed Outline(s) of Production.

2. Educate the firm on policy, processes and compliance expectations. In general, this includes the following:
    a. Sampler Training – explain the why and talk about how they can comply
        i. Submission Samples
        ii. Retention Samples
        iii. Flexibilities listed in VSM 800.59 and responsibilities
    b. Submission of Samples – use 2020 you filled out
    c. Submission of APHIS Form 2008s – use 2008 you filled out
        i. Get email for ENSR
        ii. Suggest it is a group email
        iii. This is outside of the NCAH portal
    d. Discussion regarding use of the NCAH portal –
        i. Go to NCAH Portal Guidance for CVB submitters webpage
            1. Review Step-by-Step guide on access
            2. Review User Guides for submissions
            3. Mention Training Videos
        ii. The firm may not want to be portal enabled if they are not very active. It may be more administrative upkeep than they will do.
            1. They should have the ability to check the portal weekly
            2. Remind them if they are enabled, it is for ALL CVB correspondence, including regulatory letters and AIRs which are CVB generated.
    e. Review CVB Website – VSM, Notices and CVB Procedure Manuals
        i. Encourage them to sign up for Stakeholder Notifications
        ii. Click on RED envelope on any APHIS Page and follow instructions
    f. Maintaining product and testing records – including electronic records

g. Growth promotion testing of sterility media, 9 CFR 113.25(b)
h. If the product license is restricted, discuss how to meet this restriction
i. Review expectation regarding communication on 9 CFR 116.5(b)
j. Submissions regarding extension of dating 9 CFR 114.14 (many prelicensing serials require this, so it is often one of the first submissions to CVB-IC)
k. If preparing autogenous, review expectations of 9 CFR 113.113 and VSM 800.69. They will not be allowed to use the regulatory flexibilities for adjacent, non-adjacent and isolate extensions until such time as they have demonstrated proper understanding and adequate control.
l. If preparing production platform and/or prescription platform biologics, review VSM 800.213 and VSM 800.214. The initial license that establishes the platform will be for a traditional fully licensed product, with subsequent licenses for production platform and/or prescription platform products. The firm must have an approved vector expression system (VES), a defined location and procedure for inserting the gene of interest (GOI), and a means of testing each new VES-GOI. These should be described in detail in Section I of the OP of the initial product.
    i. Ensure that the facilities are adequate for the procedures.

    ii. Discuss with firm how the different VES-GOIs will be identified (may also want to discuss inventory management, as they could quickly have a large number of different constructs). Note that new GOIs must be approved by the Reviewer and listed in the OP.

    iii. Stress that production platforms rely on a single VES, a standardized process for inserting different GOIs, and a defined manufacturing procedure. Deviations are not permitted.

m. If a foreign site, determine if the firm maintains any high consequence Foreign Animal diseases or pests and has been addressed in the risk assessment.

PROCESSES USED - Understand no question you ask is “dumb” as we are trying to understand what they are doing and how they are doing it. Usually they are “new” to regulation or at least USDA regulation. It is our opportunity to explain the “why” of the regulation, not just apply it in a black and white manner.

1. Audit production and testing records for the pivotal efficacy serial, serial(s) used in field safety testing or prelicensing serials.
    a. Determine if the critical steps have been included in the Outline of Production.
    b. Is the information listed in the Outline of Production accurately reflected in the records?
    c. Firms may use standard operating procedures (SOP). Review the SOPs to ensure the parameters listed are within the specifications listed in the Outline of Production.

2. Review the OP/SO comments made by the Reviewer and see how the firm is addressing these comments. This may be an action item.

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3. Trace product back to the Masterseed and Mastercell (if applicable).
    a. Do a physical inventory of at least a working or production seed/cell.
        i. For autogenous bacterial isolates, a complete vial may not be used for each passage, they may just use a "loop" to inoculate growth media. Determine how they account for use of these isolates.
    b. Do a physical inventory of the masterseed/cell. Ensure this is not detrimental to the material.
    c. How to they maintain Master Sequences/Master Sequence information?
        i. Synthesis record
        ii. Sequence confirmation
        iii. Most likely these are electronic records. Make sure they meet records requirements listed in 9 CFR Part 116 and VSM 800.122, Electronic Recordkeeping and Compliance with 9 CFR Part 116

4. Account for product prepared and tested – through records and physical counts
    a. Raw material
    b. In-process components
    c. Filled product, including materials used such as bottles, caps, seals, plates
    d. Testing reagents

5. Ensure equipment is calibrated and in good working order. Ensure records are maintained and the processes used are documented. Remember digital readouts must be qualified.
    a. Schematics of HVAC, air flow, and pressure differentials may be reviewed
    b. Airborne or cleanroom classifications may be reviewed
    c. Cleaning and disinfection of critical areas may be reviewed

6. Review Distribution Records – ensure system can account for product to the end user, this is sometimes overlooked by new firms and the control of product has not been formalized. In some cases the number of vials removed is handwritten on a piece of tape or on the side of the box containing final product. This is not a complete record and may be hard to ensure the record is retained after the inventory is depleted. In many cases, it is incomplete. Distribution records to review during prelicensing inspection include:
    a. Shipments to outside laboratories for testing
    b. Product used in field safety studies
    c. Samples submitted to CVB
    d. Product used for efficacy studies
    e. Retention samples

7. Shipping – sometimes they may have antidotal data for the "unlicensed" product they were previously shipping. This may not be sufficient and should be addressed prior to licensure.
    a. How do they show product was shipped under proper storage temperatures?
    b. If they intend to use a distributor, discuss how product is going to be accounted for to the user level, such as a recall situation.

8. In some cases the product may not have been made or tested so normal audit opportunities are not available.

a. Ask them how they prepare or test the product and document their answers. Compare these to the steps listed the Outline of Production.
b. Review forms prepared for use in production and testing. Compare the information to be captured to the steps listed in the Outline of Production.

9. Observe any production and testing activities that are on-going during the inspection. Many times they will not be preparing or testing product as they want to focus on the inspection.

10. Labels will not be returned until the product license is issued. Discuss process they are going to use for label control and accountability. Review any SOPs or forms they have associated with this process.

11. Discuss Adverse Event Report Process and review for sufficiency. Review Adverse Event Reporting Program on the CVB Website Page.

Post-Inspection Activities, also see CVB-SOP-0036 (formerly ICSOP0015)

Only the "long" form of the inspection report should be used for prelicensing inspections, CVB-TEM-0018 (formerly ICTEM0009). This will include descriptions of what was observed and audited, lists of VSM to reference and items that must be corrected prior to issuance of the license or permit.

Not all action items found must be corrected prior to the issuance of the license/permit. Some may be corrected at the time of the next production or testing process.

The ML with the inspection report is routed in accordance with CVB-WI-0136 (formerly ICWI0215). The PEL Reviewer receives a Notification in the ML.

Once all action items have been completed, a ML is initiated and the *Final Licensing Memo*, CVB-TEM-0020 (formerly ICTEM0012) is written. The document is routed through the Section Leader, Inspections (or acting) prior to being internally routed to the Reviewer.

1. The Type of Document is "Internally Routed".
2. All associated MLs, including the prelicensing inspection report, should be informationally linked to this ML.
3. The action items related to the prelicensing inspection should be closed.
4. The ML is moved forward for Section Leader (IC) Review.
5. When approved, the ML is moved to the Specialist who then child-loops it to the PEL Reviewer.
6. The PEL Reviewer enters the ML into the Licensing Plan and closes the child-loop.
7. The Specialist moved the ML to the BCA for finalization.
8. The ML is finalized and completed as "Workflow completed, no records management"

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