

TESTING OF BIOLOGICAL PRODUCTS

1. Overview

The United States is fortunate in that we are one of the few countries in the world to have a dedicated laboratory for regulatory agency-based testing of veterinary biological products. During the prelicense period, confirmatory testing is performed by the CVB on Master Seeds and Cells and on finished product (prelicense serials). After licensure, product testing may be performed prior to serial release (check testing), if a problem arises in the field, or at the end of product dating (stability testing). Other than check and stability testing, nearly all testing is initiated at the request of a PEL reviewer or IC specialist.

2. Samples for Testing

Before licensure, samples for testing are obtained upon request. After licensure, manufacturers are required, per 9CFR 113.3, and VSM 800.59, to submit to the CVB samples of each serial that they wish to release for distribution and sale. All samples are maintained in a repository at the CVB laboratory facility (Samples Processing Section,) for the dating period of the product. Additional samples must be retained by the manufacturer and may be obtained upon request.

3. Prelicense Testing

3.1. Master Seeds, Cells, and Sequences

See the following work instructions for details on the steps leading to confirmatory testing by the CVB laboratory.

- [4.13 Master Seed/Cells/Sequences](#)
- [5.2 Issuing a Special Request for Lab Testing of Master Seeds and Master Cells](#) [REDACTED]
- [5.3 Issuing a Special Request for Lab Testing of Prelicensing Serials, Outline Changes, or Technology Transfers](#) [REDACTED]

When confirmatory testing is performed on Master Seeds and Cells at the CVB laboratory, the Seeds and Cells may be tested in any manner deemed appropriate by the CVB. Thus, additional testing (e.g., antibiotic sensitivity for bacterial seeds, whole genome sequencing) not performed by the manufacturer may be done.

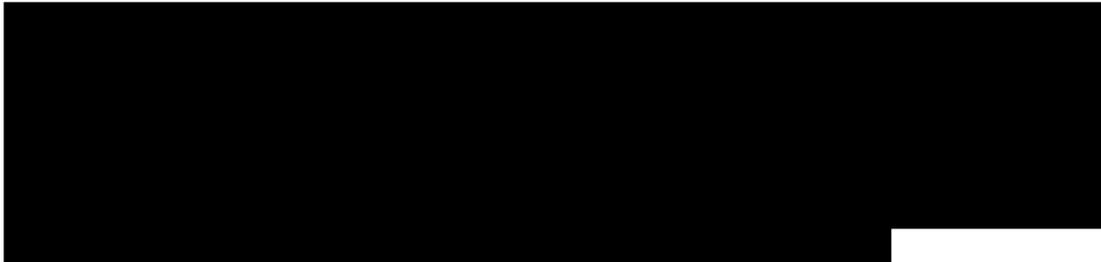
[REDACTED]

3.2. Testing of Prelicense Completed/Finished Product

As one of the final steps prior to licensure, 3 serials of product are produced. These serials must be prepared according to the filed Outline of Production and should be completely independent (should originate from separate bulk antigen lots). They should be at least 1/3 of the size of a typical production serial.

The purposes of prelicense serials include:

- Confirming the manufacturer can make the product consistently
- Confirming the manufacturer can make product without contaminating it
- Providing the CVB laboratory the opportunity to evaluate the potency assay to confirm that 1) the procedures are appropriate for the product and 2) the assay is adequately described in the OP or SO.



The serials are tested according to the specifications of Section V of the Outline of Production. The manufacturer tests the product first, submits the results to the CVB on APHIS Form 2008, and requests permission to submit samples for confirmatory testing. All serials must be satisfactory for every confirmatory test, or additional serials must be prepared and tested until 3 consecutively produced serials are satisfactory.

When reviewing 2008s of prelicense serials, ensure all of the test results are adequately described. For potency tests requiring references, ensure the reference lot number and expiration date are listed. See VS Memorandum [800.53](#) for additional requirements for APHIS Form 2008.

When 2008s have been reviewed and deemed acceptable, they should be forwarded immediately to CVB-IC through the ML. The CVB-IC uses these forms for official release of the prelicense serials after the product license is issued. **Note:** Manufacturers may submit preliminary 2008s containing incomplete information. Preliminary/incomplete 2008s are *not* to be forwarded to the CVB-IC. Forward only the final 2008.

When prelicense serials are tested by the CVB, the tests described in Section V of the Outline are performed. Extra scrutiny is given to new assays, to ensure they are adequately sensitive, specific, and rugged to serve as serial release assays. This is CVB's opportunity to evaluate new assays prior to their final approval. If concerns

arise regarding the suitability of the assays in Section V, additional testing deemed appropriate by the CVB also may be performed.

As with the number of prelicense serials, the reviewer, in conjunction with the content section leader and the lab, may elect to confirm the results of only selected Section V tests or to confirm the results on only a subset of the prelicense serials. Any reductions to the full complement of testing should be based on the firm's prior success in conducting the test(s). Note the justification for any reductions in the product licensing plan.

Prelicense testing should not be requested until all of the Section V assays are adequately described, clearly documented, and assay validation reports have been submitted and accepted. During the course of prelicense testing, the laboratory may identify additional areas for clarification/correction in the assay procedures, but **it is the responsibility of the reviewer to review the assay procedures carefully for clarity, completeness, and accuracy before they are forwarded to the laboratory.**

4. Post-license testing

As a general rule, PEL reviewers do not request testing of products after licensure, as this is the purview of CVB-IC. **Testing is warranted, however, if the manufacturer wishes to make a critical change to the Outline of Production.** The page changes should not be approved until the acceptable testing has been completed by the CVB-lab. In this case, serial(s) produced according to the proposed alteration may be held for testing before the Outline revision is approved. [REDACTED]

The laboratory may initiate random check and stability tests on routinely submitted samples. This activity generally proceeds without reviewer involvement, but it is important to understand the process in case questions or problems arise [REDACTED]

When a manufacturer submits routine post-license samples to the CVB, they are eligible to be selected for confirmatory (check) testing. The testing must be scheduled within 7 days of receipt (3 days for diagnostic test kits and other special "test and release" products). This testing serves as a check on the validity of the results submitted to the CVB by the manufacturer on APHIS Form 2008. The manufacturer is notified regarding which serials will be on test, and these serials cannot be distributed or sold until the testing is complete, with satisfactory results. [REDACTED]

[REDACTED]

Check testing, in most cases, may be performed concurrently with testing performed by the manufacturer, so it is common for manufacturers to submit test samples before they have completed testing the serial themselves. See VS Memorandum [800.55](#) for policy regarding concurrent vs. confirmatory testing.

Unless a problem exists, products are not eligible for check testing outside the initial 7- (or 3-) day window so that manufacturers will not be unfairly burdened by serials they cannot market. Also, only those tests described in Section V of the Outline are performed, and the results are evaluated strictly by the criteria in the Outline. Alternative protocols are not generally used (except in situations where the manufacturer has consented to an alternative). If laboratory personnel feel there is a problem with any of the assays, they are encouraged to contact the reviewer for that manufacturer. When a serial of a licensed product fails check test or SR test, the lab should update the reviewer regarding the issue. This provides an opportunity for the reviewer to review the assay in use and address any assay issues with the firm.

Stability testing may be performed at, or near, the end of dating for a serial of product. Serials are usually selected for testing within two months of expiration (see V.S. Memorandum [800.77](#) for policy regarding stability testing), and tested by repeating Section V potency tests. Exceptions to this, however, do occur.

[REDACTED]

5. Requesting Testing by the CVB Laboratory

5.1. Test requests and reporting are currently managed through the Licensing, Serial Release, and Testing Information System (aka LSRTIS).

When a reviewer requests testing, Special Requests (SR)s will be entered by the CVB laboratory personnel and the reviewer will be notified of the SR number. See Reviewer Manual Chapter 5.2 Issuing a Special Request for Lab Testing of Master Seeds and Master Cells for details. See 5.3 Issuing a Special Request for Lab Testing of Prelicensing Serials for details regarding requesting confirmatory testing of Prelicensing Serials.

5.2. Write a letter to the firm to authorize submission of samples for testing.

- [REDACTED] Include the test request number from LSRTIS as the “test authorization number”, as well as the IBC number for

recombinant Master Seeds. Do not authorize submission of samples for a recombinant product without an IBC number. The firms will need to reference this number/these numbers on the APHIS Form 2020 (for non-portal users) or the packing slip (for portal users), which accompanies the shipment of samples. As firms are usually anxious to submit samples, it is quite common to give verbal authorizations. In this case, do not forget to follow up with a written confirmation in a timely manner.

- Include the required list of reagents and materials as an enclosure with the authorization letter to submit samples to the laboratory.

• [REDACTED]

[REDACTED]

Please note that this differs from the process to request a new mail log number for other reasons. To have a mail log generated for any reason other than to account for a test results letter, a reviewer should request permission from a section leader, and then ask a PA to generate a mail log number.

5.3. **If a seed is considered to be an animal pathogen**, it is subject to applicable interstate shipping rules when it is shipped to the CVB laboratory for confirmatory testing. **If a seed is a select agent**, it is subject to additional shipping regulations. See the Reviewer Manual Chapter on Shipping Animal Pathogens and Select Agents for additional guidance. [REDACTED]

5.4 Include a copy of CVB's permit to receive animal pathogens for the firm to include with the shipment of Master Seeds for confirmatory testing. [REDACTED]

6. Monitoring Test Progress

[REDACTED]

7. Completed Test Reports

7.1. When tests are completed, the laboratory will enter and verify the results in LSRTIS. The VMO/Microbiologist must ensure that the CVB laboratory's results are in agreement with the requirements listed in the Outline of Production; if the results are not in agreement, the VMO/Microbiologist should explore the discrepancy. [REDACTED]

[Redacted text block]

[Redacted text block]

- [Redacted list item]
- [Redacted list item]
- [Redacted list item]
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- [Redacted list item]

7.3. When all of the testing has been completed, write a letter to the firm informing them of the results. See Appendix III for an example letter for prelicense serials. See Reviewer Manual Chapter [4.13](#), Master Seeds/Cells/Sequences for an example letter for these items. Include the following in the letter:

- Serial numbers tested
- Type of tests performed (either include in letter or enclose LSRTIS test report for external distribution)
- Test disposition (either include in letter or enclose LSRTIS test report for external distribution)
- Description of approvals, if any, including any restrictions that may be placed on the approval

7.4. Note that the official approval date for seeds/cells is the date of the response letter to the firm, not the date that the testing was completed.

Appendices attached on following pages.

[REDACTED]

[REDACTED]