Comments Due by August 12, 2019

VETERINARY SERVICES MEMORANDUM NO. 800.53 Draft No. 629

TO: Veterinary Services Leadership Team
    Directors, Center for Veterinary Biologics
    Biologics Licensees, Permittees, and Applicants

FROM: Deputy Administrator

SUBJECT: Serial Release of Licensed Biological Products

I. PURPOSE

This memorandum conveys policy and procedures to comply with title 9, Code of Federal Regulations (9 CFR), parts 113 and 116, sections 113.3, 113.6, and 116.7.APHIS prohibits a licensee or permittee from marketing a serial of licensed/permitted product until they receive notification, from APHIS, of the APHIS Disposition authorizing or prohibiting the market release or shipment of that product serial.

II. REPLACEMENT

This memorandum cancels Veterinary Services (VS) Memorandum No. 800.53, dated October 25, 2016. It is being updated to harmonize procedures for serials intended for immediate marketing, prelicense evaluation, supporting changes to the Outline of Production and technology transfers. It also clarifies that electronic submission via the National Centers for Animal Health (NCAH) Portal is the preferred method for submitting documents for support of release of biological products, serials submitted for prelicense evaluation and technology transfer requests.

III. DEFINITIONS

- **Released Product** - A finished product released [for marketing after all requirements have been satisfactorily complied with. 9 CFR 101.3(e).
- **Serial Release** – The CVB evaluation process of a serial resulting in a final APHIS Disposition.
- **APHIS Disposition** – The final decision by CVB authorizing or prohibiting a licensee or permittee to begin marketing a serial.
- **NCAH Portal** - Secure web-based electronic submissions between registered biologics licensees and permittees and the CVB. The CVB considers NCAH
Portal submissions to be an acceptable equivalent to hard-copy APHIS Form 2008 and APHIS Form 2020 submissions.

- **Authorized firm representative** - Personnel responsible for any phase of development, manufacture, or distribution of a veterinary biological product, and who have been granted access to submit official correspondence to the CVB.

IV. PROCEDURES FOR SHIPMENT AND RECEIPT OF BIOLOGICS SAMPLES (APHIS FORM 2020)

A. The CVB encourages licensees and permittees to send APHIS Form 2020 (Form 2020) from an authorized firm representative through the NCAH Portal. Form 2020 on the Biologics Forms page within the CVB Website and previous editions are also acceptable for submission as hard copies. Licensees or permittees must either generate a packing slip through the NCAH Portal or prepare a Form 2020 for each shipment of samples. A separate Form must be used for each sample type indicated in block 4 (Purpose). If the CVB requests additional samples, the licensee/permittee must use a separate Packing Slip or Form 2020 and mark “RESUBMISSION” in block 4. For more information, refer to VS Memorandum No. 800.59 or the instructions on the CVB Website for submitting an APHIS Form 2020.

1. Only employees with the Sampler role and USDA Level 2 eAuthentication are allowed to submit the information to the CVB through the NCAH Portal.

2. Alternatively, Authorized Firm Representative (authorized government samplers) may submit a paper copy of the Form 2020.

3. Send shipments of biological samples, with accompanying packing slip or Form 2020, to the following address:

   Center for Veterinary Biologics
   NVSL, Laboratory Resources Unit – Sample Processing
   1920 Dayton Avenue
   Ames, IA 50010

B. APHIS will acknowledge receipt of samples with entries in blocks 9 and 17 through 19. The CVB will return a signed copy of the Form 2020, with the assigned sample number notated, to the licensee or permittee if the licensee/permittee submitted a hard-copy Form 2020. Alternatively, the CVB will provide a response containing the assigned sample number in the NCAH Portal if the licensee/permittee submitted via the NCAH Portal.
V. PROCEDURES FOR SUBMISSION OF VETERINARY BIOLOGICS
PRODUCTION AND TEST REPORT (APHIS FORM 2008, APHIS FORM 2008A,
AND ACCEPTABLE EQUIVALENT)

A. The CVB encourages licensees and permittees to submit APHIS Form 2008
(Form 2008) from an authorized firm representative through the NCAH Portal.
Alternatively, the authorized firm representative may submit paper copies of
Form 2008 available on the Biologics Form page within the CVB Website or an
approved substitute may also be used. Forms not previously approved by the
CVB should be submitted for review and approval prior to use.

1. Only employees with the Liaison, Alternate Liaison, or Serial Release role
and USDA Level 2 eAuthentication are allowed to submit the information to
the CVB through the NCAH Portal. For more information, see Veterinary
Services Memorandum 800.63.

2. Alternatively, authorized firm representatives may submit a paper Form
2008 with an original signature, and one copy, to the following address:

   CVB – Inspection and Compliance
   USDA-APHIS-VS
   1920 Dayton Avenue
   P.O. Box 844
   Ames, IA 50010

B. The CVB considers the submission of Form 2008, 2008A, or equivalent to be
confirmation by the licensee or permittee that all manufacturing, including that
prior to Section V of the approved Outline of Production, was in compliance
with the Outline of Production and the applicable regulations.

C. When the licensees/permittees submits completed product samples in bulk form
to APHIS, a Form 2008, clearly marked as a “BULK” submission, showing the
manufacturer’s test results on bulk samples must be submitted. Receiving an
APHIS Disposition allowing the release of bulk material does not exempt a
licensee or permittee from submitting an APHIS Form 2008 for the release of
finished product.

D. Licensees and permittees must submit a Form 2008 for each completed serial or
subserial prepared. The licensee/permittee must submit all completed Forms
2008, regardless of whether the serial was intended for release immediately or in
support of product licensure, to CVB-Inspection and Compliance (CVB-IC).

E. Serials (Form 2008) Submissions Requested by CVB-Policy, Evaluation, and
Licensing (CVB-PEL)
1. Serials Prepared for Prelicensing Evaluation

Serials may be prepared for various reasons during the product licensing process, but typically three serials are prepared for prelicense evaluation that may become eligible for release when the license is issued. Firms should discuss this requirement with their CVB-PEL Reviewer in advance of serial preparation. This section does not apply to preliminary or partial data that may be requested by the CVB prior to availability of all testing data or to testing of experimental product.

For Forms 2008 meeting the above criteria, the firm representative should ensure that “Other” is marked in Block 12 and add the word “Prelicense” in remarks (Section 11). If submitting via the NCAH Portal, the firm representative should indicate the Disposition by Firm to be “Other-Prelicensing”. Reviewers in CVB-PEL will be notified when Forms 2008 have been submitted for prelicense serials. Cite the Form 2008 submission date in any subsequent related correspondence to CVB-PEL in which a copy of Form 2008 historically would have been included.

Serials made for prelicense evaluation, but not tested by CVB-PEL, are still processed by CVB-IC. Samples are still required and should be submitted as “Prelicense”.

2. Serials Supporting Outline of Production Revisions

Changes may be made to the Outline of Production after product licensure. Certain changes may not be approved by CVB-PEL until at least one serial produced and/or tested under the new method(s) has been tested satisfactorily by CVB. Such Outline changes typically include, but are not limited to, changes in Section V testing methods or material changes to manufacture that may impact product quality. Testing requirements should be discussed with the Reviewer.

When a licensee or permittee is directed by their Reviewer to provide a serial(s) for confirmatory testing to support a proposed Outline change, the Disposition by Firm on the Form 2008 for the applicable serial should be “Other-Outline Change.” As with other Form 2008, any correspondence with the Reviewer should be cited by the Mail Log number on the Form 2008.

3. Serials Supporting Technology Transfer Requests

Changes may be made to the Outline of Production for the location of where a product is produced and/or tested. Marketing of the product, which was produced and/or tested at the new location, may not occur until this change is accepted by CVB-PEL. CVB-IC may perform an inspection or request
additional documentation to substantiate the facility has the proper equipment and personnel to manufacture the product prior to the release of a serial.

When a licensee or permittee is directed by their Reviewer to provide a serial(s) for confirmatory testing and/or approval to support a proposed change to the location of where serials are produced or tested, the Disposition by Firm on the Form 2008 for the applicable serial should be “Other-Technology Transfer.”

F. Preparation of a Form 2008
A firm representative must complete the paper Form 2008 as follows (See NCAH Portal User Guide for guidance on corresponding NCAH Portal fields):

- **Block 1.** Enter the page number. For subsequent pages, use Form 2008A.

- **Block 2.** Enter the Establishment license or permit number (9 CFR, parts 102 and 104, sections 102.4(c) and 104.7(a)).

- **Block 3.** Enter the name and mailing address of the licensee or permittee.

- **Block 4.** Enter the date the final containers were filled. Enter N/A (not applicable) for bulk submissions.

- **Block 5.** Enter the Veterinary Biologics Product Code number from the current product license or permit (9 CFR, parts 101 and 102, sections 101.3(k) and 102.5(b)(3)). For prelicense serials, enter the assigned Product Code.

- **Block 6.** Enter the expiration date to be used on the final container labels. Compute the expiration date in accordance with the Outline of Production (9 CFR, parts 101 and 114, Sections 101.4(f) and 114.13).

- **Block 7.** Enter the serial or subserial number (9 CFR, part 101, sections 101.3(h) and (i) and 101.4(e)). Serial and subserial numbers are limited to no more than 15 alphanumeric characters.

- **Block 8.** Enter the true name of the veterinary biological product as stated on the current product license or permit (9 CFR, part 101, section 101.4(d)).

- **Block 9.** Enter all tests conducted to support release of the serial or subserial as defined in Section V of the Outline of Production, including No Tests and inconclusive tests. If the space in block 9 is not adequate, use Form 2008A to report additional test results.
a. **Block 9A.** Enter the test reference by entering the paragraph identification from the filed Outline of Production in which the specific test is described (e.g., V.C.2) and, if applicable, 9 CFR reference.

b. **Blocks 9B & 9C.** Enter the Started and Concluded dates for each test conducted on bulk or final product. For animal potency tests, the dates entered in 9B and 9C should be all inclusive for the complete test, including vaccination, challenge, and/or serological testing dates.

c. **Block 9D.** Enter all test results, including the validity and control requirements as described in the filed Outline of Production.

d. **Block 9E.** Insert the letter code as noted on the Form 2008 that corresponds to the test conclusion. Explain in block 11, Remarks, the basis for a "No Test" or "Inconclusive" entry.

(1) A satisfactory (S) test designation. The firm makes this final conclusion for a valid test with results that meet the release criteria stated in the filed Outline of Production or 9 CFR Standard Requirement (9 CFR, part 101, Section 101.5(l)(2)).

(2) An unsatisfactory (U) test designation. The firm makes this final conclusion for a valid test with results that do not meet the release criteria stated in the filed Outline of Production or 9 CFR Standard Requirement (9 CFR, part 101, Section 101.5(l)(3)).

(3) An inconclusive (I) test designation. The firm uses this designation for an initial test when a sequential test design established in the filed Outline of Production or Standard Requirement allows further testing if a valid initial test is not satisfactory. When the initial or any subsequent test is declared inconclusive, the reasons shall be reported in the test records, the result shall not be considered as final, and the test may be repeated as established in the filed Outline of Production or Standard Requirement. If the firm designates a test as inconclusive and the biological product is not further tested, the test designation of unsatisfactory is the final conclusion. (9 CFR, part 101, Section 101.5(l)(4))

(4) A No Test (NT) designation. The firm uses this designation when a deficiency in the test system has rendered a test unsuitable for drawing a valid conclusion. When the firm declares an initial or any subsequent test is a No Test, the reasons shall be reported in the test records, the results shall not be considered as final, and the test may be repeated. If the firm designates a test a No Test and the biological
product is not further tested, the test designation of unsatisfactory is the final conclusion (9 CFR, part 101, Section 101.5(l)(1)).

- **Block 10.** Enter the inventory of product containers or quantities to which testing and disposition apply. For serials or subserials designated as “Eligible for Release,” this quantity is the entire inventory of product prepared for marketing. For serials or subserials designated as “Destroyed by Firm,” indicate at least an estimated quantity. For imported material, enter the entire inventory of a completed serial prepared for marketing.

  a. **Block 10A.** Enter the number of containers, using a separate line for each size of container. Entities must maintain accurate accountability of product. If an inventory of product reported on the Form 2008 is inaccurate and falls outside the control limits as determined by the manufacturer, an amended Form 2008 should be submitted with a corrected inventory.

  b. **Block 10B.** Indicate the quantity in each container or the number of tests in each kit (doses, mL, or units). Enter doses for vaccines and bacterins. For product with more than one dose size, enter the maximum number of doses that could be marketed. Enter number of tests, not plates, for diagnostic test kits. Products “For Further Manufacture” (FFM) that are not shipped in final container should indicate the volume in milliliters (mL). Specify which unit of measure is being used for each entry.

  c. **Block 10C.** Enter the total quantity (10A x 10B) for each line of inventory and include the unit of measure for each size (doses, mL, or units).

  d. Total columns A and C and enter the respective totals, including the unit of measure for each (doses, mL, or units).

- **Block 11.** Place any pertinent remarks in this block.

  a. Enter information explaining the reason a test conclusion was considered a “No Test” or “Inconclusive,” as noted in block 9E.

  b. Serials of finished product which contain material from FFM serials must indicate the establishment number, Product Code, and serial number of all FFM serials contained in the finished product serial.

  c. The amount of imported product shipped for marketing in the United States should be noted. An authorized sampler at the permittee’s quarantine facility must certify the amount and condition of inventory received per shipment of product imported for sale and distribution.
Include the date the product was received at the permittee's quarantine facility. For more information, refer to VS Memorandum No. 800.101.

d. Indicate whether the submission is in support of prelicensing, a revision to the Outline of Production, or a technology transfer request.

e. Reference test results previously submitted on another subserial’s Form 2008.

f. Indicate if the submission is for a “Bulk” sample.

g. If the serial is the result of an approved reprocessing or rebottling submission, note the original Product Code and serial number.

h. If the serial is the result of an approved for inventory transfer submission, note the original establishment number, Product Code, and serial number.

i. If the serial has been reprocessed by adding one completed serial of product to another completed serial of product, note both serial numbers.

j. Indicate the identity and expiration date of all reference preparations used for potency testing of serials.

k. For autogenous biologics, include the identification of the component organisms and the host animal species for which the product is intended. See VS Memorandum No. 800.69 for further information on autogenous biologics. For Prescription Platform Products, include the information as indicated in VS Memorandum No. 800.314.

• **Block 12.** Mark the applicable firm disposition block.

a. “Eligible for Release” is a certification by the licensee/permittee that the serial is prepared and tested in accordance with the Outline of Production and is considered eligible for market release.

b. “Destroyed” is a certification of actual destruction and not the intent to destroy. Indicate the date of destruction. If destruction is for a reason other than unsatisfactory tests, state the reason in block 11.

c. “To be Reprocessed and Retested” is a request that must be approved in accordance with 9 CFR 114.18 and VS Memorandum No. 800.62.

d. Use “Other” for prelicense serials, inventory or expiration date corrections, extensions or shortening of dating, rebottling, transfer requests, serials to support Outline of Production changes, Technology
Transfers, or additional information to be filed. Provide an appropriate explanation in block 12. Additional remarks may be recorded in block 11. Note that these individual requests have their own Firm Dispositions in the NCAH Portal.

- **Block 13.** The Form 2008 and 2008A must have the original signature of a person whose authorization has been previously filed with APHIS, in accordance with 9 CFR 114.7(a) and VS Memorandum No. 800.63.

- **Block 14.** Enter the title for the person whose signature appears in block 13.

- **Block 15.** Enter the date the Form 2008 was signed.

G. **Preparation of Form 2008A.** All instructions given for Form 2008 apply to Form 2008A or acceptable substitute. Block 5 of Form 2008A is not applicable and need not be completed.

H. **If Section V testing per the Outline of Production is performed by the licensee/permittee after APHIS marketing release,** the licensee/permittee must report unsatisfactory testing to the CVB-IC in adherence to 9 CFR 116.5.

I. **CVB does not require the manufacturer to report satisfactory testing performed after marketing release to CVB-IC unless CVB requests the testing records. However, the manufacturer must maintain the testing records.**

VI. **PROCEDURE FOR DETERMINATION OF AN APHIS DISPOSITION**

CVB uses the serial release process to review test summaries related to the purity, safety, potency or efficacy of each serial and subsequently provides an APHIS Disposition to the firm. This section is applicable to product serials manufactured after the product is licensed/permited. It also applies to those prelicense serials, produced shortly before licensure is granted, that subsequently may become marketable after the product is licensed/permited.

A. **CVB-IC will examine the final results of the licensee/permittee on a Form 2008 and will evaluate whether a serial meets the criteria with testing requirements within the Outline of Production or Standard Requirement(s). The licensee/permittee will be notified of the necessary corrections or additions if exceptions are noted. CVB-IC may use the Audit and Correction Transmittal for this purpose. Once CVB-IC makes a determination whether the licensee/permittee is authorized to market or ship the serial, an authorized representative of CVB-IC signs the Form 2008. This signed form (whether on the Form 2008 or electronically) is the exclusive documentation of CVB’s marketing authorization. If release is not authorized or is subject to restrictions, CVB-IC provides an**
explanation on the APHIS Form 2008. CVB-IC may also provide additional information for action by the licensee/permittee.

1. Market Serials Not Selected for Testing. CVB-IC will document its decision to authorize or prohibit marketing of a serial which the CVB-PEL Laboratory has not tested, by selecting an APHIS Disposition in blocks 16 through 19 on the APHIS Form 2008.

2. Market Serials Selected for Testing

   a. The CVB-PEL Laboratory may select any serial of a licensed product for testing, but it must make a decision whether to test a specific serial within 7 full calendar days after receipt and processing of representative samples of that serial from the firm. The CVB-PEL Laboratory has 3 full calendar days after receipt and processing of a specific diagnostic test kit sample to make a decision whether to test that specific sample.

   b. CVB-IC may select a serial of a licensed product for testing beyond the 3 or 7 calendar day selection period after sample receipt. CVB-IC may notify licensees and permittees whenever such exceptions occur.

B. CVB-IC will document its decision to authorize or prohibit the release of a product serial in blocks 16 through 19 on the Form 2008. See Section IX.C and IX.D for the APHIS Dispositions that authorize and prohibit marketing or shipment of a serial.

C. Distribution. CVB-IC will retain the completed original Form 2008. CVB-IC will send one completed copy of the Form 2008, with additional documentation, as applicable, to the licensee or permittee. Likewise, CVB-IC will notify the licensee or permittee by means of the NCAH Portal.

VII. CENTER FOR VETERINARY BIOLOGICS-LABORATORY TEST REPORTS

A. Preparation and Processing

   1. Serials for Marketing. The CVB-PEL Laboratory will report test results to CVB-IC on each serial or subserial tested. Supplementary reports will be appended if additional data and explanatory comments, beyond those included on a standard report, are warranted.

   2. Serials Involved in Prelicensing Evaluation, Outline of Production Revisions, and Technology Transfer. The CVB-PEL Laboratory will report test results to CVB-PEL with supplementary reports, if indicated. CVB-PEL will make recommendations to the CVB-IC on the final APHIS disposition.
B. Distribution. CVB-IC will send completed test report to the licensee or permittee. APHIS will retain copies, as appropriate.

VIII. EXCEPTIONS

A. First Serial Autogenous Biologics

1. Refer to VS Memorandum No. 800.69.

2. If the disposition of the serial is “Destroyed By Firm” (DBF), the date of final disposition and the reason the serial was destroyed should be included in the “Remarks” column.

3. The licensee/permittee must make test results for specific serials available to CVB on request.

IX. ELECTRONIC NOTIFICATION OF MARKETING AUTHORIZATION (SERIAL RELEASE)

A. Electronic same-day notification for final APHIS Disposition of serials is provided. This notification process will be used for all Forms 2008 received by CVB, if the licensee/permittee has provided an e-mail address for this purpose. See Appendix I for an example electronic notification.

1. A licensee or permittee will receive e-mail notification from APHIS-CVB Serial Release, cvb.serialrelease@usda.gov, for each Form 2008 processed by the CVB. The e-mail notifications may be any APHIS disposition, including notifications that a serial is not eligible for marketing. The recipient is responsible for review of the APHIS disposition and appropriate action based on the market status of the serial as determined by APHIS.

2. The establishment may market the product in accordance with the final disposition designated by APHIS on receipt of the electronic notification.

3. There is no U.S. regulatory requirement that a signed hard-copy of the Form 2008 must be physically at the manufacturing site before shipping an approved serial. The electronic notification is the official notification for marketing purposes.

B. The following statement will be included on each electronic notification:

This electronic notification is equivalent to an APHIS Form 2008 signed by an Authorized APHIS Representative and is appropriate for marketing authorizations.
C. APHIS Dispositions authorizing the market release or shipment of serials are as follows:

1. Not to be Tested
2. Tests Completed Satisfactory
3. Shorten Dating Approved
4. Other – Release for Further Manufacture
5. Other – Serial Released for Market
6. Other – Subsequent Shipment Approved (for permitted product)
7. Other – Conditional Release Granted
8. Prelicense – Test Completed Satisfactory

D. The following APHIS Dispositions prohibiting the market release or shipment of the serial:

1. Test Completed UNSATISFACTORY
2. Shorten Dating DENIED
3. Other – UNSATISFACTORY Based on Firm’s Results
4. Other – Serial NOT RELEASED FOR MARKET
5. Other – Subsequent Shipment DENIED
6. Prelicense – EXPIRED
7. Prelicense – Tests completed UNSATISFACTORY

E. If licensee/permittee submits a hard-copy APHIS Form 2008 for processing, the signed hard-copy Form 2008 and related CVB test reports will be returned to the licensee/permittee’s mailing address. CVB performs these mailings once a week. Only one route of submission should be used per serial submission.

F. CVB uses electronic notification for audit and correction transmittals. Conditions of release (Serial Release Requirements) will be noted within the electronic notification, if applicable.

X. IMPLEMENTATION/APPLICABILITY

Updated policy in this memorandum is effective immediately.
Appendix I

U.S. Department of Agriculture
Animal and Plant Health Inspection Services
Veterinary Biologies Marketing Notification

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<th>Name, Mailing Address of Licensee or Permitee</th>
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<tr>
<th>True Name of Product</th>
<th>Product Code</th>
<th>Serial Number</th>
<th>Expiration Date</th>
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<th>APHIS Disposition Date</th>
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<tr>
<td>August 24, 2016</td>
<td>Not to be Tested</td>
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Authorized APHIS Representative - William Huls, Biologics Specialist

This electronic notification is equivalent to an APHIS Form 2008 signed by an Authorized APHIS Representative and is appropriate for marketing authorizations. See Veterinary Services Memorandum 800.53, Release of Biological Products for more information.

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