ROSEMARY SIFFORD

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VS Memorandum (VSM) 800.69

Guidelines for Autogenous Biologics

1. Purpose and Background

This memorandum describes the procedures and guidelines for interpreting the requirements for autogenous biologics at title 9, *Code of Federal Regulations* (9 CFR), sections 113.113, 113.3(b)(8), and the administrative terminology in section 101.2.

The Animal and Plant Health Inspection Service (APHIS) published the Standard Requirement for Autogenous Biologics in the *Federal Register* on April 3, 2002; the requirement became effective May 3, 2002. The Director, Center for Veterinary Biologics, Inspection and Compliance (CVB-IC), is authorized to make all decisions relating to the discretionary authorities assigned to the Administrator in 9 CFR 113.113, except 113.113(c)(2)(iv), which requires approval by the CVB Policy Evaluation and Licensing (PEL) Director.

Pursuant to the Congressional Review Act (5 U.S.C. § 801 et seq.), the Office of Information and Regulatory Affairs designated this [action] as a non-major rule, as defined by 5 U.S.C. § 804(2).

2. Document Status

A. Issue Date: 11/22/2021

B. This document replaces VSM 800.69, dated September 26, 2016.

3. Reason for Reissuance

CVB is reissuing this memorandum to:

- Inform licensees that autogenous isolates may be used for sixty (60) months without requesting permission from CVB-PEL and will be evaluated for use beyond sixty (60) months by CVB-PEL without the need to conduct an immunogenicity study.
- Include distribution of autogenous products to third-party cold storage facilities prior to final herd distribution.
- Address requirements for approval of the production of autogenous products for export only.
- Notify licensees that shipments to adjacent and nonadjacent herds will be permitted, provided the information cited in 9 CFR 113.113(a)(2) and (3) is on file

with the licensee prior to the shipment of an autogenous product for use in a herd other than the herd of origin.

4. Authority and References

A. Authorities

- 9 CFR 101
- 9 CFR 113
- 9 CFR 114
- 9 CFR 116

B. References

- VSM 800.53, Release of Biological Products
- VSM 800.56, Disposal of Unsatisfactory and Undesirable Materials
- VSM 800.59, Veterinary Biological Product Samples
- VSM 800.65, Eggs and Chickens for Production of Veterinary Biological Products
- VSM 800.85, Avian Influenza Vaccine
- VSM 800.103, Reissuance of Product Licenses for Autogenous Products and Guidance Concerning Restrictions on the Production and Use of Veterinary Biologics
- VSM 800.109, Master Seed and Master Cell Stock Testing Report Submission

5. Audience

VS employees and members of the biologics industry.

6. Guidance

A. Approval of Nonveterinarian Specialist

9 CFR 113.113 allows an autogenous biologic to be prepared for use by a person of specialized expertise other than a veterinarian in special situations if approved by the Administrator. CVB-IC uses professional judgment in determining whether the person has the appropriate expertise to administer the product and deal with possible medical problems associated with use of an autogenous biologic. Communicate the following information to CVB-IC when requesting approval to prepare an autogenous biologic for use by a nonveterinarian:

1. *Identification*. Name and qualifications (e.g., training, role in diagnosing the disease condition) of the nonveterinarian.

2. *Justification*. Description of the special situation (e.g., animal species involved, location, disease condition[s]).

B. Determination of Date of Isolation

9 CFR 113.113(a)(4) states that the microorganism used for the production of an autogenous biologic may not be older than fifteen (15) months from the date of isolation or twelve (12) months from the date of harvest of the first serial of product produced from the microorganism(s), whichever comes first. This verbiage has historically caused confusion regarding the interpretation of the date of isolation and the concomitant initial isolate dating. For purposes of streamlining and clarifying the initial isolate dating period, all isolates may be used for an initial dating period of fifteen (15) months from the date of harvest of the first serial of product produced from the microorganism(s).

C. Cells Used for Production

1. *Primary Cells*. These should satisfy the requirements set forth in 9 CFR 113.51 and VSM 800.65 (if Specific Pathogen Free eggs are used). The appropriate citations should be included in the Outline of Production (Outline).

2. *Cell Lines*. These should satisfy the requirements prescribed in 9 CFR 113.52 and VSM 800.109 and be identified in the filed Outline. Since cell lines can be used to produce products for multiple animal species, the Outline must list the species for which the cell line is approved.

D. Extension on Use of Autogenous Isolate

9 CFR 113.113(a)(4) allows extended use of an isolate beyond fifteen (15) months from the date of isolation; however, this original dating period for isolate usage does not have any particular basis in fact, and, as noted in Section 6.B., has historically been a source of confusion. Therefore, extensions of isolate usage to sixty (60) months from the date of harvest of the first serial of product produced from the microorganism(s) will be permitted when requested by the attending veterinarian or nonveterinary specialist responsible for assessing the health needs of the herd of origin. Documentation of the continued need for use of the isolate does not require submission to CVB; however, the justification should be maintained on file for CVB's review upon inspection. CVB-PEL will evaluate extensions for isolate use beyond sixty (60) months. Extension requests must include the following information:

1. *Assessment of Continued Involvement*. A current assessment of the continued involvement of the originally isolated microorganism(s) with disease in the herd, including diagnostic work done to support this assessment.

2. *Documentation of Satisfactory Performance.* Provide documentation from the attending veterinarian or nonveterinary specialist to support that the previous use of the autogenous biologic was beneficial. In addition, provide the number of

doses administered and an assessment of any and all adverse events associated with the use of the biologic along with the request for extension of isolate usage beyond sixty (60) months.

3. *Inactivation kinetics.* Review of inactivation procedures for products propagated in a manner susceptible to the introduction of viral contamination. To ensure the safety of isolate usage, inactivation methods used for the isolates being extended must demonstrate the ability to completely inactivate possible "worst case scenario" viral contaminants. This requirement will be for products grown in cell culture, eggs, or other methods capable of introducing viral contaminants, and will only apply to limited bacterial products such as those propagated in cells. The inactivation study must demonstrate complete inactivation of the proposed species-matched viral isolate at a level of 10^5 $TCID_{50}$/ml.

    a. For autogenous swine products, the surrogate contaminating virus is porcine circovirus.

    b. For autogenous poultry products, the surrogate contaminating virus is chicken anemia virus.

    c. For autogenous bovine products, the surrogate contaminating virus is bovine parvovirus.

    d. For autogenous products used in species other than swine, poultry, or bovines, firms could use one of the listed viruses, or propose an alternative for CVB consideration.

    The inactivation study must be conducted in a manner acceptable to CVB. Submit protocols to CVB for review prior to initiating the studies. Approved studies must be on file for the autogenous license under which the isolate will be used. The study must be cited in the approved Outline of Production associated with the isolate usage. In cases where more than one inactivation method is allowed under the Outline of Production, only an inactivation method supported by the data outlined in this Section may be used on extended use isolates. These studies are one-time-only requirements and may be conducted preemptively and independently of any need for extended isolate usage. Firms with approved inactivation studies currently on file with CVB in their autogenous product Outlines should check with CVB to see if those studies will be sufficient to meet this requirement for the intended purpose of isolate extension.

4. *History of Product*. Date and place of isolation of microorganism(s) and date of harvest of first serial.

5. *Veterinarian/Client/Patient Relationship*. Licensees are responsible for certification of a valid veterinarian/client/patient relationship by the veterinarian requesting the product, as defined by the American Veterinary Medical Association policy, "Principles of Veterinary Medical Ethics." For the approved nonveterinarian specialist, supply equivalent information for CVB's evaluation.

E. Disposition of Outdated Isolates

Microorganisms used to prepare autogenous biologics shall not be maintained in a licensed establishment beyond the time authorized for use in production. Handle outdated isolates in accordance with 9 CFR 114.15 and VSM 800.56. Maintain records of the disposition of isolates as provided in 9 CFR 116.

F. Definition of "First Serial"

A serial is considered a "first serial" if it is the first serial of autogenous biologic produced (i.e., prepared and eligible for shipment to the customer) from a new isolate or isolates, or if the first batch of autogenous culture produced from a new isolate is added to fractions produced from previously used isolates.

1. *Age of Isolation*. The serial must not include any culture that is over the age limit.

2. *Removal of Isolates*. Removing an isolate from a previous autogenous biologic formulation does not make the modified product a "first serial"; it is automatically a subsequent serial.

G. Reporting of Autogenous Biologics

1. *First Serials*. The first serial of an autogenous biologic produced from an unrestricted isolate (see VSMs 800.85 and 800.103 for antigens not authorized for production under an autogenous license) may be released for shipment by the firm on the basis of satisfactory results of third-day observations of tests, in accordance with 9 CFR 113.113(c)(1).

   Once testing is complete, but no longer than thirty (30) days from completion of testing, submit a test summary to CVB. Since the implementation of the National Centers for Animal Health (NCAH) Portal, use of the summary format has diminished and will no longer be used to report first serials.

2. *Subsequent serials*. All serials, other than the first serial, made from unrestricted organisms. Submit Veterinary Biologics Production and Test Report information (APHIS Form 2008) to CVB-IC for each subsequent serial of autogenous biologics. In lieu of the APHIS Form 2008, the information may be submitted through the NCAH Portal, if the manufacturer has the appropriate access. This information will

be reviewed and processed as outlined in VSM 800.53. Do not ship subsequent serials prior to approval from CVB-IC.

3. *Serials produced with restricted microorganisms*

   a. To ensure that the use of autogenous veterinary biologics does not interfere with animal disease surveillance and/or control and eradication programs and does not pose other health risks, the use of certain microorganisms is restricted. See VSMs 800.85 and 800.103 for a list of restricted organisms.

   b. Do not produce autogenous biologics from restricted organisms without CVB approval.

   c. All (first and subsequent) serials of autogenous biologics that contain restricted organisms are released by the standard procedure described in section 6.G.2.

H. Definition of Serial Size and Sample Submission/Retention

The number of final containers in a serial or subserial is determined by the number of containers in inventory for release (i.e., available for sale). Do not submit samples of first serials of autogenous products, regardless of serial size, to CVB unless requested. Submit samples of subsequent serials filled in >50 containers to CVB in accordance with 9 CFR 113.3(b)(8).

1. *Number of Samples to Select*. Based on the number of containers produced, allocate samples as follows:

   a. For serials with ≤50 containers, the firm selects two (2) government reserve samples only. This applies to first serials and subsequent serials.

   b. For first serials with >50 containers, the firm selects ten (10) government reserve samples only. After the autogenous summary has been returned to the manufacturer, two (2) government reserve samples must be retained.

   c. For subsequent serials with >50 containers, select ten (10) samples; however, submit only two (2) samples to CVB and hold two (2) as government reserve samples. The remaining six (6) samples may be returned to inventory, based on VSM 800.59.

2. *Sampling Procedures*. Select samples of all autogenous biologics in accordance with 9 CFR 113.3(b)(8). The licensee or permittee must hold reserve samples in accordance with 9 CFR 113.113(e)(4) and submit them to CVB only when requested.

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I. Retesting of Autogenous Serials

First serials shipped after the third day of observation of purity test cultures and of safety test animals must be immediately recalled in the event of an inconclusive or unsatisfactory test result. CVB-IC must be immediately notified in the event of a product recall. The serial may be retested to rule out technician error. The retest must be completed and satisfactory before the serial can be released for continued shipment.

J. Shipment of Autogenous Products

1. The licensee or permittee is permitted to ship the autogenous serial to the veterinarian or approved nonveterinarian specialist for whom the product was prepared.

2. With appropriate documentation, autogenous serials may be shipped directly to an owner or a third-party cold storage distribution facility for final distribution if approved by the veterinarian or nonveterinarian specialist ordering the autogenous serial. In the case of the third-party cold storage facility, prior permission to use the storage facility must be received from CVB-IC on a one-time basis. Once approved, these cold storage facilities are considered subject to unannounced inspections as deemed necessary to ensure compliance with the autogenous product distribution regulations. However, the licensee or permittee is ultimately responsible for all third-party adherence to the regulatons and this privilege may revoked at any time based on cause. Finally, serial distribution records must be readily available or maintained by the licensee or permitee for CVB-IC review.

3. Shipments to adjacent and nonadjacent herds will be permitted, provided the information cited in 9 CFR 113.113(a)(2) and (3) is on file with the licensee before an autogenous product is shipped for use in a herd other than the herd of origin.

4. For purposes of product distribution, the herd of origin includes all animals of the same species and under common ownership regardless of the physical location of the individual herds. Autogenous serials for distribution to the herd of origin as described above are exempt from the records required for adjacent or nonadjacent herds provided the autogenous manufacturer has an approved inactivation kinetics study (or studies) on file with CVB and cited in the approved Outline for the autogenous license under which the product was produced as described in Section 6.D.3. above. This requirement is independent of any issues related to isolate dating. Manufacturers choosing not to perform the cited inactivation kinetics studies will not be afforded this new regulatory flexibility for intrastate and interstate movement and distribution of autogenous products

within the herd of origin, and must fulfill all the requirements historically required for adjacent and nonadjacent distribution of autogenous biologics as cited in 9 CFR 113.113(a)(2) and (3).

K. Autogenous Products for Export Only Distribution

Manufacturers with an autogenous license are allowed to produce autogenous products for export only purposes.

1. Obtain a valid Organisms and Vector (Form 16-3) permit to import the organism.
2. Depending on the situation and country of origin, CVB may also request a risk analysis for importation.
3. With CVB approval, the isolate can be moved into the production facility.
4. Autogenous products containing isolates originating from outside the United States are not eligible for use or distribution within the United States regardless of any potential epidemiological link with the foreign herd of origin. These autogenous products are only eligible for "export only" distribution.
5. The manufacturer's internal records should clearly document this distribution restriction.
6. Limitations on the organisms eligible for autogenous products are the same as for domestic products.

7. Short Guide to Autogenous Biologics

A. Limit on Use of an Isolate

1. The autogenous isolate may be used for fifteen (15) months from the date of harvest of the first serial of product produced from the microorganism(s).
2. Extended use of isolates to sixty (60) months from the date of harvest of the first serial of product produced from the microorganism(s) will be permitted when requested by the attending veterinarian or nonveterinary specialist. No approval from CVB is required for this extension, but records must document an ongoing need.
3. CVB-PEL evaluates extensions for use beyond sixty (60) months. Extension requests must include the information prescribed in 9 CFR 113.113(a)(4) as further clarified in this Memorandum.
4. Disposition of Outdated Isolates. All outdated isolates shall be handled in accordance with 9 CFR 114.15 and VSM 800.56. Maintain records of the disposition of isolates as provided in 9 CFR 116.

B. Permissible Cells

Tested primary cells or approved cell lines may be used in production, as indicated in the Outline.

C. First Serial

1. A first serial may be shipped after three (3) days of satisfactory testing.
2. CVB does not require samples of first serials.
3. Firms should recall serials if tests are inconclusive or unsatisfactory.
4. Submit APHIS Form 2008 to CVB-IC, as listed in 6.G.1 of this memorandum, within thirty (30) days of testing completion. NCAH Portal submission is also acceptable.
5. Identification of the organism should be sufficient to determine it as the causative agent.

D. Second and Subsequent Serials

1. Second and subsequent serials must be tested under the general requirements in 9 CFR 113.100 or 113.200 to include purity, safety, and identification (genus and species for bacteria; family for virus) with the exception that poultry products must be safety tested in poultry using the format specified in 9 CFR 113.116(b) and 113.117(b). All killed virus vaccines (except for poultry vaccines) shall be safety tested in guinea pigs or mice. However, products for use in fish or other aquatic species, or reptiles, are exempt from this requirement and shall be tested in the species for which the product is recommended or an appropriate surrogate species as described and approved in the Outline of Production. Complete all testing and submit APHIS Form 2008 information to CVB-IC for release. Hard copy APHIS Form 2008 or NCAH Portal submission is acceptable.
2. Samples are submitted to CVB unless the serial is <50 containers. Confirmatory testing by CVB may occur. For serials of <50 containers, two reserve samples are held and may be requested by CVB.
3. APHIS must release the serial BEFORE it is shipped.

E. All Serials from Restricted Microorganisms

1. CVB must approve production of autogenous biologics from organisms restricted in VSM 800.103.

2. Submit APHIS Form 2008 for each serial (first and subsequent) of autogenous biologics produced from restricted microorganisms to CVB-IC. APHIS must release the serial before shipment. In lieu of the APHIS Form 2008, the information may be submitted through the NCAH Portal if employees at the manufacturer have received the appropriate access.

8. Implementation/Applicability

Updated policy in this memorandum is effective immediately.