August 30, 2002

VETERINARY SERVICES MEMORANDUM NO. 800.69

Subject: Guidelines for Autogenous Biologics

To: Biologics Licensees, Permittees, and Applicants
State Veterinarians
Director, National Veterinary Services Laboratories, VS
Directors, VS Regions
Directors, Center for Veterinary Biologics
Area Veterinarians in Charge, VS

I. PURPOSE

To describe present procedures and guidelines for interpretation of the requirements for Autogenous Biologics under the provisions of Title 9, Code of Federal Regulations (9 CFR), Section 113.113, 113.3(b)(8), and the administrative terminology in Section 101.2. To inform licensees and permittees that they may start using a summary form to report first serials of autogenous products 30 days after the publication of this memorandum.

II. CANCELLATION

Veterinary Services (VS) Memorandum 800.69, dated October 29, 1985, is hereby canceled.

III. BACKGROUND

The Standard Requirement for Autogenous Biologics was published in the Federal Register on April 3, 2002, and 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 permitted the Administrator in 9 CFR 113.113, except 113.113(c)(2)(iv), which requires approval by the Center for Veterinary Biologics-Licensing and Policy Development (CVB-LPD).

IV. GUIDELINES

A. Approval of Non-Veterinarian Specialist

Section 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 will use 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. The licensee or permittee should communicate the following information to CVB-IC when requesting approval to prepare an autogenous biologic for use by a non-veterinarian:

1. *Identification* - Name and qualifications (i.e., training, role in diagnosing the disease condition) of the non-veterinarian.

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

B. Determination of Date of Isolation

Section 113.113(a)(4) states that the microorganism used for the production of an autogenous biologic may not be older than 15 months from the date of isolation.

1. *Date of Isolation* - The date of isolation will be considered as the date the organism was first identified as the causative agent of the disease, whether the identification was done by the attending veterinarian, approved non veterinarian specialist, or by a diagnostic laboratory.

2. *Record of Date of Isolation* - The licensee or permittee should request the isolation date from the veterinarian or the approved non veterinarian specialist ordering the autogenous product and maintain a record of such information available for review on APHIS inspection.

C. Cells Used for Production

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

2. *Cell Lines* - These should satisfy the requirements prescribed in 9 CFR 113.52 and be identified in the filed Outline of Production or in a Special Outline (SO). Since cell lines can be used to produce products for multiple animal species, the Outline or SO must list the types of products for which the cell line is approved.

D. Extension on Use of Autogenous Isolate

Section 113.113(a)(4) allows extended use of an isolate beyond 15 months from the date of isolation. Extensions to 24 months will be evaluated by CVB-IC. Information needed from the firm requesting such an extension includes, but is not limited to:

l. *Identification of the Microorganism* - Genus, species, and strain/serotype for bacteria; family and type for viruses. Some bacteria that should be serotyped include: *Salmonella sp., Erysipelothrix sp., Actinobacillus pleuropneumoniae, Clostridium perfringens, Pasteurella multocida, Streptococcus suis,* and *Escherichia coli*. Beta-hemolytic *Streptococcus sp.* should be further identified by their Lancefield group. Information on viruses should include the pertinent serotype/subtype/strain [i.e., Massachusetts (Mass) type of infectious bronchitis virus] For *C. perfringens*, proof of toxin production should be submitted.

2. *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.

3. *Documentation of Satisfactory Performance* - Documentation to demonstrate that previous use of the autogenous biologic was beneficial. This may consist of showing that commercially licensed products do not provide equivalent protection.

4. *Assessment of Adverse Reactions* - Assessment of any and all adverse reactions associated with the use of the biologic.

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

6. *Veterinarian/Client/Patient Relationship* - Certification of a valid veterinarian/client/patient relationship by the veterinarian requesting the product. For the approved non veterinarian specialist, equivalent information should be supplied for evaluation.

Extensions beyond 24 months are evaluated by CVB-LPD. In addition to the information listed above, immunogenicity data and a proposed potency test must be submitted.

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. Outdated isolates must be handled in accordance with 9 CFR Section 114.15 and VS Memorandum 800.56. Records of the disposition of isolates must be maintained as provided in 9CFR Section 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(s) 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* - All of the isolates used to produce a serial must be within 15 months of the date 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 (Please refer to VS Memorandum 800.103 and 800.85 and CVB Notice 02-04 for antigens not authorized for production under a 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). Its manufacture and testing is subsequently reported in a summary format.

Separate summaries must be prepared for each product code. First-serial summaries must be submitted to CVB-IC after 25 serials of a given product code have been produced, or quarterly, whichever occurs first. Quarterly reports should be submitted no later than the 21st day of January, April, July, and October (Fiscal year basis due to reports).

An example of an autogenous first-serial summary is found in Appendix I, but alternative formats also are acceptable. Summaries must include the following information:

a. Header Information

(1) Establishment license or permit number,

(2) Address of production facility,

(3) Product code (One product code per summary form)

b. For each serial prepared, include the following information in a horizontal (line item) format:

(1) Serial number - As shown on final container

(2) Isolate Code(s) - Enter a code for each microbial fraction in the serial. See Appendix 2 for a list of standard codes. If no code is shown for the microorganism, enter the full name of the microorganism. If the antigen is covered by VS Memorandum 800.103 or 800.85 or CVB Notice 02-04, the serial is not eligible for reporting via the summary format.

(3) Expiration date,

(4) Number of containers,

(5) Doses produced,

(6) Remarks.

(a) Destroyed serials--All serials are assumed to have been released for shipment unless otherwise indicated in the Remarks section. Enter the date destroyed and the reason for destruction.

(b) Retested serials--If the serial is retested by the firm, enter the reason for the retest. Please refer to 9 CFR 113.113(c)(iii) and 9 CFR 116.5 for user related actions and APHIS notification.

c. The bottom of the summary report must include signature, title, and date blocks for firm and APHIS representatives.

2. *Subsequent serials*--All serials, other than the first serial, made from unrestricted organisms

a. A Veterinary Biologics Production and Test Report (APHIS Form 2008) must be submitted to CVB-IC for each subsequent serial of autogenous biologics. These will be reviewed and processed as outlined in VS Memorandum 800.53, Release of Biological Products. Subsequent serials are not to be shipped prior to approval by 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 VS Memorandum 800.103 and 800.85 for a list of restricted organisms. Additional organism-specific guidance may be found in CVB Notices (e.g., CVB Notice 02-04 for influenza virus in turkeys).

b. Autogenous biologics must not be produced from restricted organisms without approval from APHIS.

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

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). No samples of first serials of autogenous products, regardless of serial size, will be submitted to APHIS unless requested. Samples of subsequent serials filled in >50 containers must be submitted to APHIS in accordance with 9 CFR 113.3(b)(8).

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

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

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

c. For subsequent serials with >50 containers, 10 samples must be submitted to APHIS and 2 must be held as government reserve samples.

2. *Sampling Procedures* - Samples of all autogenous biologics must be selected 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 APHIS only when requested.

I. Retesting of Autogenous Serials

First serials that were 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 unsatisfactory test result. CVB-IC must be immediately notified in the event of a product recall. They may be retested to rule out technician error. The retest must be completed and satisfactory before the product can be released again.

J. Shipment of Autogenous Products

The licensee or permittee is permitted to ship the autogenous serial to the veterinarian or approved non veterinarian specialist for whom the product was prepared. With appropriate documentation, autogenous serials may be shipped directly to an owner if approved by the veterinarian or non veterinarian specialist. Shipment to adjacent and non-adjacent herds may only occur after approval by CVB-IC. The information cited in 113.113(a)(2) and (3) must be submitted, reviewed and approved by CVB-IC before an autogenous product may be used in a herd other than the herd of origin. Records and documentation pertaining to shipments of autogenous biologics should be maintained for APHIS inspection.

V. SHORT GUIDE TO AUTOGENOUS BIOLOGICS

A. Limit on Use of an Isolate

1. 15 months from isolation, or

2. 12 months from harvest, whichever is shortest.

3. Extended use of isolates requires CVB approval.

B. Disposition of Outdated Isolates

All outdated isolates should be handled in accordance with 9 CFR Section 114.15 and VS Memorandum 800.56. Records of the disposition of isolates must be maintained as provided in 9CFR Section 116.

C. Permissible Cells

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

D. First Serial

1. Permissible to ship after 3 days of satisfactory testing.

2. No samples to APHIS needed.

3. Recall if tests are not satisfactory.

4. Submit APHIS Summary Form to CVB-IC as listed in Section G of this Memorandum.

5. Identification of the organism should be sufficient to determine it as the causative agent.

E. Second and Subsequent Serials

1. 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).

2. Complete all testing and submit APHIS Form 2008 to CVB-IC for release.

3. Samples are submitted to APHIS unless the serial is <50 containers. Confirmatory testing by APHIS may occur. For serials of <50 containers, 2 reserve samples are held and may be requested by APHIS .

4. APHIS must release the serial **BEFORE** it is shipped.

F. <u>All serials from restricted microorganisms</u>

1. Production of autogenous biologics from organisms restricted in VS Memorandum 800.103 must be approved by the CVB.

2. APHIS Form 2008 for each serial (first and subsequent) of autogenous biologics produced from restricted microorganisms must be submitted to CVB-IC, and the serial must be released before shipment.

/s/ W. Ron DeHaven

Ron DeHaven
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Veterinary Services

2 Enclosures

Appendix 1. Example of Autogenous Summary Format

Est. _____ Address:_____ Product Code _____

Serial No.	Isolate Code(s)	Exp.Date	Number of Containers	Doses produced	Remarks

Firm signature	title	date
APHIS signature	title	date

Appendix 2. Isolate codes for use on Autogenous summary sheets

ADENO	adenovirus
APLEUR	*Actinobacillus pleuropneumoniae*
ASUIS	*Actinobacillus suis*
ACTPY	*Actinomyces pyogenes*
AERSAL	*Aeromonas salmonicida*
AERSOB	*Aeromonas sobria*
ARCPY	*Arcanobacter pyogenes*
AEV	avian encephalomyelitis
BCER	*Bacillus cereus*
BAVIUM	*Bordetella avium*
BBRONC	*Bordetella bronchiseptica*
BVDV	bovine viral diarrhea virus
BRAN	*Branhamella species*
BRANOXIS	*Branhamella oxis*
CPSIT	*Chlamydia psittaci*
CDIFF	*Clostridium difficile*
CPERF	*Clostridium perfringens*
CAMFET	*Campylobacter fetus*
CAMJUJ	*Campylobacter jejuni*
CPSEUD	*Corynebacterium pseudotuberculosis*
ENTERO	enterovirus
EAERO	*Enterobacter aerogenes*
EFAEC	*Enterococcus faecalis*
EHDV	epizootic haemorrhagic disease virus
ERHUS	*Erysipelothrix rhusiopathiae*
ECOLI	*Escherichia coli*
FCOM	*Flavobacterium columnare*
FPSY	*Flabobacterium psychophilium*
FMAR	*Flexibacter maritimus*
HPGALL	*Haemophilus paragallinarium*
HPSUIS	*Haemophilus parasuis*
HSOM	*Haemophilus somnus*
HFW	hairy foot wart
HEV	hemorrhagic enteritis virus
HV	herpes virus

IBV	infectious bronchitis virus
IBDV	infectious bursal disease virus
KAZA	*Klebsiella azaenae*
KOXY	*Klebsiella oxytoca*
KPNEUM	*Klebsiella pneumoniae*
LBAC	*Lactobacillus spp*.
LLACT	*Lactococcus lactis*
LMONOC	*Listeria monocytogenes*
MHAEM	*Mannheimia haemolytica*
MBOV	*Moraxella bovis*
MOVIS	*Moraxella ovis*
BROVIS	*Moraxella (Branhamella) ovis*
MYCO	*Mycoplasma spp.*
MYALK	*Mycoplasma alkalescens*
MYARG	*Mycoplasma arginini*
MYBOVI	*Mycoplasma bovigenitalium*
MYBOVS	*Mycoplasma bovis*
MYHYOP	*Mycoplasma hyopneumoniae*
NDV	Lentogenic Newcastle disease virus
ORNITH	*Ornithobacterium rhinotracheale*
PAPV	papilloma virus
PMV	paramyxovirus
PAERO	*Pasteurella aerogenes*
PHAEM	*Pasteurella (Mannheimia) haemolytica*
PMA	*Pasteurella multocida*, Type A
PMD	*Pasteurella multocida*, Type D
PHDAM	*Photobacterium damselae*
PEV	porcine enterovirus
PRRS	porcine reproductive & respiratory syndrome virus
PSEUDO	*Pseudomonas* spp.
REOV	reovirus
AREOV	avian reovirus
SAL	*Salmonella* spp.
SMAR	*Serratia marcescens*
SHPUT	*Shewanella putrefaciens*

SAUR	*Staphylococcus aureus*
SCHR	*Staphylococcus chromogene*
SSEPID	*Staphylococcus epidermidis*
SHAE	*Staphylococcus haemolyticus*
SHYIC	*Staphylococcus hyicus*
SINT	*Staphylococcus intermedius*
SWAR	*Staphylococcus warneri*
SXYL	*Staphylococcus xylosus*
SAGAL	*Streptococcus agalactiae*
SBOVII	*Streptococcus bovis*
SDYSGA	*Streptococcus dysgalactiae*
SEQUI	*Streptococcus equi*
SEQSIM	*Streptococcus equisimilis*
SPOR	*Streptococcus porcinu*
SSSUIS	*Streptococcus suis*
SUBER	*Streptococcus uberis*
SZOOEP	*Streptococcus zooepidemicus*
SIV	swine influenza virus
TGE	transmissible gastroenteritis virus
VANG	*Vibrio anguillarum*
VCAR	*Vibrio carchariae*
YPSE	*Yersinia pseudotuberculosis*
YRUCK	*Yersinia ruckeri*