September 20, 2002

VETERINARY SERVICES MEMORANDUM NO. 800.65

Subject: Eggs and Chickens for Production of Veterinary Biological Products

To: Biologics Licensees, Permittees, and Applicants
Directors, Center for Veterinary Biologics

I. PURPOSE

This memorandum provides guidance on preparing veterinary biological products that use embryonated chicken eggs or chicken tissue as an ingredient. It is meant to assist licensees, permittees, and applicants in meeting the purity and quality requirements in 9 CFR 113.50.

II. CANCELLATION

This memorandum cancels Veterinary Biologics Memorandum No. 800.65 dated December 22, 1999.

III. BACKGROUND

Purity and quality requirements for ingredients of veterinary biological products are specified in 9 CFR 113.50. Specific ingredient requirements for each licensed product are found in the applicable Outline of Production or Special Outline. This memorandum defines the infectious agents which should be excluded from eggs and chickens used in the production of veterinary biological products without specifying the methods by which a source flock should be established or maintained. It also recommends procedures for the management and disposition of eggs and chickens following a disqualifying disease outbreak in a source flock. Information is also provided on interpretations of a specific test in terms of reporting the results on an APHIS Form 2008.

IV. PURITY AND QUALITY RECOMMENDATIONS

A. Source Flock

For the purposes of this memorandum, the term "source flock" will be defined as the flock maintained for the production of embryonated SPF eggs. If the embryonated eggs are hatched to produce SPF birds for the production of infectious bursal disease

vaccine, these birds are considered part of the source flock and should be free of **any** clinical signs of infectious disease.

B. Agents of Concern

The licensee or permittee should maintain records to demonstrate that each lot of embryonated chicken eggs or chickens used for production of veterinary biological products has been derived from an unvaccinated flock free of the following infectious agents as demonstrated by negative serology:

1. Avian adenoviruses; groups I (serotypes 1-12), II, and III
2. Avian encephalomyelitis virus (AE)
3. Avian influenza virus (AI), type A
4. Avian reovirus (Reo)
5. Infectious bronchitis virus (IB); Massachusetts, Connecticut, Arkansas,and JMK strains
6. Infectious bursal disease virus (IBD)
7. Laryngotracheitis virus (LT)
8. Lymphoid leukosis virus (LL); subgroups A, B, and J
9. Marek's disease virus (MD); serotypes 1, 2, and 3
10. Newcastle disease virus (NDV)
11. Reticuloendotheliosis virus (REV)
12. *Mycoplasma gallisepticum*
13. *Mycoplasma synoviae*
14. *Salmonella gallinarum*
15. *Salmonella pullorum*
16. Other agents deemed inappropriate by APHIS

C. Clinical Signs in a Source Flock

In the case of eggs or tissue culture derived from eggs, the licensee or permittee should document that the source flock is negative for lymphoid leukosis antigen (subgroups A, B, and J), negative for clinical signs of fowlpox, and negative on environmental culture for *Salmonella* spp. In the case of birds used for production, they should be free of clinical signs of any infectious disease. An agent causing clinical signs or seroconversion in production birds is referred to as a disease agent. Disqualifying agents or disease agents are to be treated in a similar fashion for disease outbreaks.

D. Source Flock Monitoring

The licensee or permittee should describe, in a filed Outline of Production or Special Outline, the methods and frequency of source flock monitoring and the test methods used.

E. Procedures for Handling Eggs and Chickens

Once introduced into the licensed establishment, licensees and permittees should handle eggs and chickens for the production of veterinary biological products in a manner to maintain their pathogen-free status. The licensee or permittee should describe such handling procedures in an addendum to the facility blueprints and legends.

V. DISEASE OUTBREAKS

A. Notification of Disease Outbreaks

The licensee or permittee should require the source flock owner to notify them within 24 hours of a positive test indicating the presence of a disqualifying disease or any disease agent causing clinical signs in a source flock (including birds used for the production of infectious bursal disease virus fractions). If a disqualifying disease or disease agent is discovered in a source flock, the licensee or permittee should notify the Center for Veterinary Biologics-Inspection and Compliance (CVB-IC) within 24 hours.

B. Determining the Period of Suspect Eggs and Birds

In the event of a disease outbreak in a source flock used for the production of embryonated eggs, CVB-IC will set the date of initial seroconversion for the flock at l day after the collection of the last negative sera and notify licensees and permittees of the date by letter. In the event of the appearance of clinical signs in production birds, CVB-IC will set the date of initial infection on a case by case basis and notify licensees and permittees of the date by letter. This letter will indicate the Veterinary Biologics Investigation (VBI) number assigned to the outbreak and request an accounting of all suspect eggs and chickens received by the firm. The period of suspect eggs should be the 2 weeks prior to the seroconversion date for NDV, avian adenovirus, and *Salmonella*; the 3 weeks prior to the seroconversion date for IB and *Mycoplasma*; and the 4 weeks prior to the seroconversion date for AE, AI, LL, REV, and Reo. There is no suspect egg period for LT, IBD, MD, or Pox. The suspect period for the production birds will be determined on a case by case basis.

C. Disposition of Suspect Materials

At first notification of a disease outbreak or clinical signs within a source flock, licensees and permittees should take the following actions:

1. *Uninoculated Eggs, Chickens, and Cell Cultures* - Discard all suspect eggs, chickens, and cell cultures derived from suspect eggs if they have not yet been inoculated with production seed.

2. *Inoculated Eggs, Chickens, and Cell Cultures* - If already inoculated with production seed, discard suspect eggs, chickens, and cell cultures derived from suspect eggs, or continue in production provided the product is appropriately tested and the presence of the disqualifying or disease agent cannot be demonstrated. (See E below for testing information.)

D. Eggs from Recovered Source Flocks

Licensees and permittees may be permitted to use eggs from a source flock which has recovered from a disqualifying disease outbreak for the production of inactivated products, provided the product is appropriately tested and the presence of the disqualifying agent cannot be demonstrated. (See E below for testing information.)

E. Testing for Disqualifying or Disease Agents

Appropriate testing depends on the disqualifying or disease agent. CVB-IC will send a testing protocol to licensees and permittees with its letter notifying them of the seroconversion or infection date following any given outbreak.

1. *Test Methods* - Testing for disqualifying or disease agents could include, but would not be limited to, the following methods:

a. For live products, licensees and permittees should attempt to isolate the disqualifying or disease organism from bulk or final container samples of the completed product.

b. For killed products, licensees and permittees should attempt to isolate the disqualifying or disease organism from samples of the bulk harvest material prior to inactivation.

c. For both live and killed products, licensees and permittees should attempt to detect seroconversion to the disqualifying or disease agent in chickens inoculated with bulk or final container samples of the completed product.

2. In order for a test result to be considered valid, the appropriate positive and negative controls should be used.

3. *Reporting Test Results* - Licensees or permittees should report results of tests for disqualifying or disease agents conducted on serials of product produced from suspect eggs or chickens to CVB-IC on the APHIS Form 2008.

a. If the serial prepared from the suspect eggs or chickens is tested and does not show signs of contamination in a valid test, record the following information:

(1) In the remarks section (section 11), record the VBI number assigned to the suspect eggs or chickens used to produce the serial.

(2) In the test data section (section 9), record the test result as "S".

(3) In the disposition section (section 12), check "other" and add the statement: "Request release based on no evidence of contamination".

b. If the serial prepared from the suspect eggs or chickens is tested and shows signs of contamination in a valid test, record the following information:

(1) In the remarks section (section 11), record the VBI number assigned to the eggs or chickens used to produce the serial.

(2) In the test data section (section 9), record the test result as "U".

c. If the serial prepared from the suspect eggs or chickens is tested and the validity requirements have not been met, record the test result as "NT". If the results can not be concluded as satisfactory or unsatisfactory, a retest is allowed, and the result of that specific test should be listed as "I".

VI. PRODUCTION OUTLINES

All Outlines of Production and Special Outlines for products which use embryonated eggs or chicken tissue as an ingredient should conform to this memorandum.

/s/ W. Ron DeHaven

W. Ron DeHaven
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Veterinary Services