USDA
United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

1400 Independence Ave, SW

Washington, DC 20250

VETERINARY SERVICES MEMORANDUM NO. 800.121

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

FROM: Jack A. Shere /s/ Jack Shere on June 21, 2017
Deputy Administrator

SUBJECT: Autologous Therapeutic Biologics

I. PURPOSE

This memorandum provides guidance on licensing autologous therapeutic biologics.

II. BACKGROUND

Advances in technology have allowed preparation of custom vaccines against individual cancers and other diseases in animals. These technologies make use of consistent manufacturing systems to manipulate samples from patients to create individualized treatments. Examples include, but are not limited to, autologous cancer therapies.

These are veterinary biological products as defined in title 9, *Code of Federal Regulations* (9 CFR), part 101.2. The unique and individualized product characteristics have necessitated adaptations to the licensure process.

III. DEFINITIONS

For the purpose of this memorandum, the following definitions apply.

Autologous therapeutic biologic. A veterinary biological product prepared for an individual animal under a prescription written by a licensed veterinary practitioner. The product consists of unique antigens or genetic sequences derived from cells or tissues of the animal, for use as a treatment against individual cancers and other diseases in animals. Autologous therapeutic biologics act primarily through the immune system or immune response.

Consistent manufacturing system. A manufacturing process relying on appropriate, controlled, and documented procedures to prepare serials differing only with respect to the patient source of cells, tissues, or genetic material.

Autologous. Derived from the same individual (i.e., involving one individual as both donor and recipient).

IV. POLICY

The Center for Veterinary Biologics (CVB) will consider applications for licensing autologous therapeutic biologics produced by a consistent manufacturing system. Initially, the autologous therapeutic biologic will be distributed as an experimental biological product until definitive data to support consistent manufacturing, safe use, and an expectation of efficacy allow qualification for licensure as an Autologous Prescription Product.

A. The initial application should include establishment and product applications listed in Veterinary Services (VS) Memorandum No. 800.50 and the following:

1. Scientific theory. Demonstration that the mechanism of action for the proposed product is immunologically driven, supported by scientifically sound theory and peer-reviewed scientific literature.

2. Proof of concept. Reports of product use, in which raw safety and efficacy data are submitted in electronic format. Refer to the CVB Web site for additional information on proper submission of reports (VS Memorandum No. 800.200) and data formats.

3. Outline of Production. The manufacturing method must be well controlled, detailed, and submitted according to the attached Outline template. Refer to 9 CFR 114.8 and VS Memorandum No. 800.206 for additional information.

B. The CVB will determine the acceptability of the product concept. If accepted, the CVB will regulate the product and manufacturing procedure as an experimental product under 9 CFR 103.3 until sufficient data establish a record of safe use and a reasonable expectation of efficacy.

1. Following notification of acceptability by the CVB, the applicant should submit the following to the CVB for authorization to ship the product:

a. A protocol describing data acquisition during the experimental product stage. This must include:

(1) The specific data that will be gathered from each patient. Indicate the minimum number of animals to be treated for each animal species and the type or types of cancer for which efficacy and safety will be evaluated. The number for each indication should be included, if applicable.

(2) Criteria for determining product efficacy.

(3) Criteria for assessing product safety.

(4) How the product will be tested prior to distribution, including quantitation of the active component.

b. The informed consent form that each client or animal owner must sign prior to receiving the experimental product.

c. Experimental labels consistent with 9 CFR 103.3 (i.e., no trade name or efficacy claims) but which do not need to state the product is not for sale. Beneath the True Name (Autologous Prescription Product), the product shall be further described as "Experimental {species} {cancer type or animal disease} Treatment" (e.g., Experimental Canine Melanoma Treatment) or "Experimental {species} Cancer Treatment," as supported by scientific theory, proof of concept, or submitted data.

d. Marketing and promotional information. Product advertising and marketing is limited to notification of availability of the autologous therapeutic biologic for treatment of a cancer or specific disease, must be targeted only to licensed veterinarians, and must be approved by the CVB prior to use.

e. Annual authorizations from proper officials in each State in which the product will be distributed.

2. Upon satisfactory review of the items in IV.B.1, the CVB will issue an authorization to distribute the experimental biological product, according to provisions specific to the product, for 1 year. A separate shipping authorization from the CVB is not required prior to shipping each serial. Instead, submit quarterly distribution reports to the CVB no later than the 21st day of January, April, July, and October. Include the serial identification, animal species for which the serial was manufactured, doses shipped, testing conducted, and any adverse events reported. Any additional State authorizations may be submitted at this time.

3. At the end of the year, submit a progress report describing safety and efficacy data collected to date. Refer to the CVB Web site for additional information on proper submission of reports (VS Memorandum No. 800.200) and data formats. The authorization to distribute experimental product may be renewed for another year if additional data are needed. The CVB expects sufficient data to be generated to support licensure within 2 years, but extensions may be requested.

4. Distribution of experimental biological product

    a. Experimental product is distributed exclusively at the request of a licensed veterinarian. A request for product must include patient signalment, pertinent diagnostic information, and the plan of treatment. The licensed veterinarian is responsible for maintaining and documenting the veterinarian-client-patient relationship consistent with the State's Veterinary Practice Act.

    b. Clients/owners must sign the CVB-approved informed consent form prior to patient treatment.

    c. Product must be labeled with the CVB-approved experimental label.

    d. The CVB may conduct an onsite inspection to evaluate the consistent manufacturing system.

    e. If a firm does not comply with 9 CFR 103.3 or misrepresents the product, the CVB may take any actions deemed necessary, including revocation of the authorization to distribute product.

C. When the necessary data have been generated to support licensure, the CVB may issue a license for Autologous Prescription Product, product code 9PPX.XX. This will be a special license with many characteristics of a conditional license.

1. A separate license is issued for each consistent manufacturing system.

2. The license will be issued for 2 years and is renewable if there are no safety or efficacy concerns.

3. Labeling must indicate the use is subject to the discretion of the prescribing licensed veterinarian, and must disclose that efficacy cannot be assured. Once a license for Autologous Prescription Product is issued, Trade Names for this class of prescription product will be allowed.

4. Serial Release Testing

    a. Purity testing is conducted according to the procedures in 9 CFR 113.26(b), with modifications available on request for product manufactured in limited amounts. Modifications should be specified in the Outline of Production.

    b. A fully validated potency test is not required for Autologous Prescription Products, but the active component must be quantified to demonstrate batching consistency.

5. The licensee is exempted from furnishing to the CVB representative samples of each serial prepared. Reserve samples must be selected and maintained by the licensee as required in 9 CFR 113.3(e), with modifications available on request for product manufactured in limited quantities. Modifications should be specified in the Outline of Production.

6. Marketing and promotional materials must be reviewed by the CVB prior to publication or distribution. This will be a license restriction. Efficacy claims cannot be advertised.

7. Additional license restrictions:

    a. Distribution in each State shall be limited to authorized recipients designated by proper State officials, under such additional conditions as these authorities may require;

    b. For use under veterinary supervision/prescription.

8. A separate serial release action by the CVB is not required prior to shipping each serial. Instead, submit quarterly distribution reports to the CVB no later than the 21st day of January, April, July, and October. Include the serial identification, animal species for which the serial was manufactured, doses shipped, testing conducted, and any adverse events reported.

VI. IMPLEMENTATION/APPLICABILITY

This policy is effective immediately.

Appendix I. Outline of Production Format for Autologous Therapeutic Biologics

I. Composition of the Product

A. Source and Type of Raw Material

II. Preparation of Product

A. Each Step of Preparation to the Completion of the Finished Product in True Containers

1. Methods Used

2. Composition of Preservative, Adjuvant, or Stabilizer, and Proportions Used; Stage and Method of Addition

a. Preservative
b. Adjuvant
c. Stabilizer
d. Other

3. Standardization of the Product

4. Serial Production

a. Assembly of Units to Make a Serial
b. Volume of Average Serial
c. Volume of Maximum Serial
d. Other Pertinent Information

5. Volume of Fill for Each Vial Size

6. Method and Technique of Filling and Sealing of Final Containers

7. Amount of Antigenic Material per Dose in Final Containers

III. Testing

A. Purity

B. Safety

C. Potency (Batching Consistency)

D. Other Tests

E. Additional Pertinent Information

IV. Post Preparatory Steps

A. Form and Size of Final Containers in Which the Product is to be Distributed

B. Collection and Storage of Representative Samples. Indicate at which steps in the production these samples are taken.

C. Expiration Dating

D. Recommended Use, Dosage, and Route of Administration

E. Site or Sites of Manufacture

F. Exemption from Freedom of Information Act or Confidentiality Statement