



Animal and Plant
Health Inspection
Service

Veterinary Services

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VETERINARY SERVICES MEMORANDUM 800.213

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

FROM: for Jack A. Shere
Deputy Administrator

SUBJECT: Licensing Guidelines for Production Platform Technology-Based, Non-Replicating, Nonviable Vaccines

I. PURPOSE

This memorandum provides guidance to licensees, permittees, and applicants for licensing non-replicating, nonviable biological veterinary vaccines. Such vaccines are prepared for use in the target species by means of production platform-based Master Seeds and Sequences with a standardized method of veterinary biological manufacture.

II. CANCELLATION

This memorandum replaces Veterinary Services (VS) Memorandum No. 800.213 dated April 29, 2015.

III. BACKGROUND

A production platform is a manufacturing process that relies on a single vector or expression system (“backbone”) and a standard process for inserting a gene or genes of interest (GOI) into the system to generate different recombinant Master Seeds or Sequences, which are then used to produce product following a standardized method for manufacture. These production platforms may be based on, but are not limited to, RNA expression systems, DNA cloning vectors, or various virus, plant, insect, or bacterial expression vectors. The GOI may consist of one or more complete or partial gene sequences. Platform-based Seeds, Sequences, or antigens are blended with excipients in a fixed formulation to manufacture completed products with certain defined properties. Examples of completed products include vaccines containing virus-like particles, nucleic acid, a killed agent, or a subunit protein or proteins prepared from an expression vector.

The Center for Veterinary Biologics (CVB) will consider streamlined regulatory requirements for licensing platform-based, standardized products resulting in non-replicating, nonviable completed products once an applicant has successfully licensed one product using the same platform and product formulation.

IV. DEFINITIONS

- A. Vector or Expression System (VES). System used to express the GOI, whether *in vivo* or *in vitro*, e.g., a baculovirus system, a nucleic acid delivery system, or a virus that is itself an immunological fraction.
- B. Gene of Interest (GOI). Full or partial gene coding for the targeted antigen, e.g., the influenza hemagglutinin (HA) gene.
- C. GOI Variant. A nucleotide sequence variant from the initial GOI, e.g., Orf2 from strain A or strain B.
- D. Construct. Combination of VES and GOI (or GOIs).
- E. Platform Product. Any one or several of a group of products that are based on the following components:
 - 1. The VES, including all reagents, seeds, sequences, and cells to propagate the final construct.
 - 2. The inserted GOI, including a defined procedure for creating new VES/GOI constructs with different sequence variants of the GOI.
 - 3. Standardized manufacturing system for consistency in the manufacture and formulation of biological product.
 - 4. Efficacy data for the initial VES/GOI construct (minimum age, dose volume, specific route of administration, specific species, minimum antigenic dose).
 - 5. Maximum antigenic content - the total amount of antigenic material per dose in a completed serial, as determined by a measurable quantity (titer, μg , etc.).
 - 6. Field safety data for the initial VES/GOI construct (minimum age, dose volume, specific route of administration, specific species, maximum antigenic content).
- F. Initial Product. A fully-licensed product that establishes the product platform, including the standardized method of manufacture, maximum antigenic content, permissible species for use, minimal age, dose, and route of administration.

V. GUIDELINES

A. Licensing Requirements

1. To establish the platform, an applicant is required to have a full product license for each specific GOI, with a defined standardized manufacturing process, and claims for use of the product administered by the given dose and route in the given species at the recommended age. Requirements typically include, but are not limited to, submission of a Category IV Summary Information Format (SIF) and Risk Assessment for the VES/GOI construct; confirmatory testing of the Master Seed (MS), Master Sequence (MSQ), and/or Master Cell Stock (MCS) by the CVB; an inactivation kinetics study; efficacy studies for each label claim; dilution of preservative study; potency assay; confirmatory testing of prelicense serials by the CVB; and a full field safety study. Specific requirements will depend on the VES system that is used. The applicant must fully describe the production method and location for generating the recombinant Master Seed or Sequence in the Outline of Production or Special Outline. The applicant cannot initiate the field safety study until the CVB has evaluated the VES/GOI construct for compliance with the National Environmental Policy Act (NEPA) and reaches a finding of no significant impact (FONSI).

Once the applicant has established a production platform and the initial product has been licensed, licensure of products containing GOI sequence variants can typically be streamlined based on some of the studies conducted with the initial product, provided there are no changes in manufacture. Subsequent constructs must be produced with the identical VES, using the exact method documented in the Outline of Production for the initial product. There should be no changes to the manufacturing process or maximum antigenic content (as determined by pre-inactivation titer or other measurable quantification of antigen), and the product label claims will be for the same species, age, and route of administration. Any change to the standardized method of manufacture, regardless of perceived impact, must be evaluated by the CVB prior to incorporation of the change and may require the establishment of a new Initial Product.

Each subsequent VES/GOI construct should be identical to the initial product construct, with the exception of the sequence of the GOI. If the initial product does not contain the full GOI, subsequent VES/GOI constructs should include a comparable region of the sequence. For approval of each new sequence variant, the CVB will require, at a minimum, evidence of field relevance, demonstration of a reasonable expectation of efficacy, submission of a Category IV SIF with the sequence to the CVB, and confirmatory testing of the new variant GOI MS or MSQ by the CVB. All safety and efficacy studies must have been conducted using product manufactured in accordance with the currently approved Outline of Production. Reevaluation for compliance with NEPA, an inactivation kinetic study, and a field safety trial are generally not needed.

If the applicant demonstrates efficacy of a construct containing a new GOI variant, the CVB will issue a full product license for the new variant. In contrast, if the applicant demonstrates a reasonable expectation of efficacy, a conditional product license will be issued. A GOI variant that is initially marketed under a conditional license can be converted to a full product license at a later date if pivotal efficacy is subsequently demonstrated and a validated potency assay is approved.

2. In cases where a full license already exists, if the applicant demonstrates that the production platform requirements are met as stated above, the CVB may allow that product to serve as the initial product establishing the platform for the defined VES/GOI.
3. The CVB considers the substitution of either a different GOI from the same initial pathogen or a GOI from a different pathogen into a VES that is used in a licensed product to be a new platform; therefore, the CVB requires a new full license to establish that VES/GOI combination. Depending on the components of the new platform, abbreviated studies for licensure may be allowed, including, but not limited to, reduced field safety requirements.
4. The CVB will subject the applicant's request for additional claims for use of a licensed platform product, either in a different species or for a different age or route of administration in the same species, to the same considerations as any traditionally licensed product, and will require efficacy and field safety studies.
5. Licensing and eligibility requirements for conditional licenses are set forth in title 9, *Code of Federal Regulations* (9 CFR), part 102.6, and in VS Memorandum No. 800.75. Platform products are subject to the same eligibility rules as any other product. In contrast to non-platform products, if the platform product meets an urgent need, then the CVB may issue or reissue a conditional license for a production platform product, even though a full license has been granted for a similar product. Products containing any of the approved sequence variants for the same GOI, for which a reasonable expectation of efficacy has been demonstrated, can be manufactured under a single conditional license.
6. The CVB may issue both conditional and full licenses for platform products containing multiple fractions based on the same VES, provided there is no immunological interference between the fractions.

7. Split manufacturing between two or more licensed firms is acceptable under the guidelines of VS Memorandum No. 800.61. In this case, the initial platform product must be licensed under the split manufacturing arrangement; a production platform that has been established by a single firm cannot subsequently be produced under a split manufacturing arrangement. Likewise, a production platform that has been established under a split manufacturing arrangement cannot subsequently be transferred to one of the firms as the sole manufacturer.
8. A licensee is prohibited from sublicensure of an established platform to another Establishment. Each manufacturer must establish the production platform independently through full licensure.
9. The CVB subjects platform products to the same license restrictions as analogous, traditionally licensed products.

B. Manufacturing Considerations

1. The CVB requirements for MSs, MSQs, and MCSs involved in a platform product are the same as those for traditional products and encompass testing by or for the firm, submission of a report documenting the test procedures and results, and confirmatory testing by the CVB. In addition, the CVB may need confirmatory testing by the CVB for the VES and/or additional seeds, sequences, or cells used in the generation of new VES/GOI constructs. The applicant must submit a Category IV SIF for each final construct and should include an electronic file of the sequence of the inserted GOI and flanking region. Each construct should be given a running number for that specific VES/GOI and should be identified with the file name “Est No._Product Code_FirmIdentity_xxx”.
2. The applicant must make all VES/GOI constructs in facilities located within the United States, the District of Columbia, the Territories, or any place under the regulatory jurisdiction of the United States. Constructs may be made within a licensed facility, in a firm’s research and development facility, or by a third party, as long as an acceptable, consistent method for the generation of new constructs is used that has been approved by the CVB.

C. Outlines of Production

1. In section I of the Outline of Production (or a cited Special Outline) for the initial product, the applicant should include a detailed description of how and where new constructs containing sequence versions of the GOI are made and the testing that is done on each new construct.

2. In Outlines of Production for subsequent VES/GOI versions, the applicant should identify the product that was used to establish the platform and should describe how each new construct was made in section I. In the Outline, the applicant may cite the Outline of the initial product for the manufacturing processes. The CVB does not allow deviations in manufacture.
3. In section I of the Outline of Production for VES/GOI versions that are conditionally licensed, the applicant should list each approved construct, the sequence designation, and the date and Mail Log No. of the approval. The applicant should identify each construct based on that VES/GOI by a running number. In addition, the applicant should provide a table in section VI.C. listing the identity number of the construct, the claims that were approved for that construct, and the date and Mail Log No. of the approval(s).
4. The applicant should include annotated maps of all vectors that are used in the production platform in an appendix to the Outline of Production.

D. Final Product Testing

1. The applicant must provide a validated potency assay for the initial product VES/GOI and for any subsequent VES/GOI sequence variant for which a full license is issued. A suitable test for batching consistency is acceptable for conditionally licensed products for which a reasonable expectation of efficacy has been demonstrated.
2. The applicant must provide an identity test to confirm that the correct VES/GOI sequence version is in the completed serial; this may be part of the potency assay (or batching consistency test) or may be an independent assay. For products that contain two or more different VES/GOI fractions, the identity test should confirm that each of the desired fractions is present in the final product. Depending on the nature of the product, the identity test may be conducted on the final product or on the bulk.

E. Labeling

1. The CVB requires that labels for all products that have a full license (the product that established the production platform, and subsequent VES/GOI sequence variants for which full efficacy was demonstrated and a validated potency assay has been approved) conform to 9 CFR 112 and the guidance provided in VS Memorandum No. 800.54. The product compilation summary that is published on productdata.aphis.usda.gov must contain the efficacy data that was approved for the specific construct and the field safety data for the initial product that established the platform.

2. The CVB requires that labels for the products that have a conditional license (subsequent VES/GOI sequence variants for which only a reasonable expectation of efficacy was demonstrated) conform to 9 CFR 112 and the guidance provided in VS Memorandum No. 800.54. Since serials containing different conditionally licensed sequence variants may be produced under the same product license, the applicant should place the statement “Sequence Variant No. ____” directly under the True Name. This number is the running identification number for the given VES/GOI sequence variant, and this is a fillable field to communicate to the end user which GOI variant is in the serial. If desired, the applicant may submit individual labels for specific VES/GOI sequence variants that contain information related to that specific sequence variant; in this case, the mounting sheet must identify the sequence variant for which that label would be used. The product compilation summary that is published on productdata.aphis.usda.gov will reference the field safety data for the initial product that established the platform and will include a statement that the product was licensed based on a production platform.

VI. IMPLEMENTATION/APPLICABILITY

This policy applies to all non-replicating and nonviable biological vaccines based on a platform product. The CVB reserves the right to determine the suitability of the proposed platform product and its use. The CVB will base its consideration on the disease agent; animal and public health concerns; and, the impact on the environment, disease surveillance, and commerce.

This memorandum is effective immediately.