



VETERINARY SERVICES MEMORANDUM NO. 800.213

Animal and Plant
Health Inspection
Service

Veterinary Services

1400 Independence
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Washington, DC
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To: Veterinary Services Leadership Team
Directors, Center for Veterinary Biologics
Biologics Licensees, Permittees, and Applicants

From: John Clifford
Deputy Administrator

**JOHN
CLIFFORD**

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Subject: Licensing Guidelines for Production Platform-Based, Non-Replicating,
Nonviable Products

I. PURPOSE

This memorandum provides guidance to licensees, permittees, and applicants for licensing non-replicating, nonviable biological products using production platform-based Master Seeds and Sequences.

II. REPLACEMENT

This memorandum replaces Veterinary Services (VS) Memorandum No. 800.213 dated August 12, 2013.

III. BACKGROUND

A production platform is a manufacturing process that relies on a single “backbone” and a standard process for inserting a foreign gene or genes into the backbone to make different recombinant Master Seeds or Sequences. These production platforms may be based on, but are not limited to, RNA expression systems, DNA cloning vectors, or various virus, plant, or bacterial expression vectors. The inserted gene or genes may consist of the complete or truncated sequence. Platform-based Seeds are then blended with excipients in a fixed formulation to manufacture completed products with certain standardized 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 advantages of producing standardized products with platform-based Seeds or Sequences include faster responses to changing and emerging pathogens and vaccines with greater immunogenic specificity. 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. POLICY

- A. The first license application for a given production platform is subject to the same licensing requirements as any other product. The applicant must also submit a category IV Summary Information Format (SIF) and a Risk Assessment adequately addressing the non-viability of the completed product. The field safety study cannot be conducted until CVB issues a finding of no significant impact (FONSI).
- B. Following licensure of an initial product using a given production platform and standard product formulation, the inserted gene or genes may be exchanged with gene variants of the same pathogen without requiring additional field safety studies, reevaluation for compliance with the National Environmental Policy Act, or evaluation of inactivation kinetics before licensing the subsequent product. The original gene or genes and subsequent gene variants may be marketed concurrent with the latest gene variants throughout the term of the license. Inserting gene variants will require evidence of field relevance, demonstration of a reasonable expectation of efficacy, and submission of the sequence to CVB. The identity of the new sequence will be included in the Outline of Production formatted as: Est No._Product Code_FirmIdentity_000.

CVB considers the addition of a different gene to a licensed production platform a new product and requires a new license. Analogous products created by inserting different genes from the initial pathogen, or genes from a different pathogen, may have reduced field safety requirements, depending on the pathogen and construct. Otherwise, the initial product for each production platform/pathogen/gene combination is subject to the same licensing requirements as non-platform products.

- C. Licensing and eligibility requirements for conditional licenses are set forth at title 9, *Code of Federal Regulations* (9 CFR) section 102.6 and VS Memorandum No. 800.75. Platform-based products are subject to the same eligibility rules as any other product. In contrast to non-platform products, a conditional license may be issued for a production platform product for which a full license has been granted for a similar product if the production platform-based product meets an urgent need. Also, conditional licenses may be issued for production platform products containing multiple fractions produced from the same platform, even if the other fractions are already part of licensed products. These multi-fraction products may be granted a conditional license if there is no material immunological interference between fractions. These products will be issued a license for 2 years, subject to renewal per 9 CFR 102.6 and VS Memorandum No. 800.75.
- D. Licensees possessing a license for a platform-based product may apply for a separate product license for Prescription Products prepared in the same manner, issued for 2 years subject to renewal. A Prescription Product may be produced for a licensed veterinarian as a custom formulation for use in a specific population of animals, based on disease risks in the herd, surrounding areas, and distant areas serving as

sources for new members of the herd. The licensed practitioner assumes responsibility for the efficacy of the prescribed product, and the manufacturer is responsible for purity and safety.

Prescribing veterinarians may submit relevant isolates or sequences to be incorporated into custom platform-based Seeds once the USDA-licensed establishment verifies the identity of the seeds or sequences. Multi-fraction products may be prescribed if each fraction is produced according to the same production platform. Custom fractions may be combined with fractions approved for use in a non-prescription product. Interference studies are not required. Additional details regarding Prescription Products are found in the Appendix.

V. IMPLEMENTATION/APPLICABILITY

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

Appendix
Prescription Products

1. *Sequence homology*: Custom vaccine Seeds or Sequences may vary minimally from a submitted nucleotide sequence to optimize expression. The goal is 100 percent homology at the amino acid sequence level, but some discretion is permitted based on agent and conditions.
2. *Adjuvant and excipients*: The prescription product is restricted to the adjuvant system and the excipients in the licensed production platform.
3. *Labeling*:
 - 3.1. Efficacy – Must disclose that efficacy has not been determined.
 - 3.2. Must contain the following statement – This is a prescription product. Recommended use shall be at the discretion of the prescribing veterinarian.
4. *Serial Release Testing*:
 - 4.1. Purity and Safety – Same as for licensed product on which prescription product eligibility is based.
 - 4.2. Potency – A fully validated potency test is not required for prescription products, but there must be testing to ensure batching consistency. The results must be reported on APHIS Form 2008.
 - 4.3. Sequence – The sequence and method of verification is reported on APHIS Form 2008.
5. *License Restrictions*:
 - 5.1. Trade names and trademarks shall not be used with this product.
 - 5.2. Marketing and promotional materials are restricted. Prescription products may not advertise efficacy claims.
 - 5.3. This license does not authorize production, distribution, or shipment of prescription vaccines for foot-and-mouth disease, rinderpest, any H5 or H7 subtype of avian influenza, any subtype of avian influenza in chickens, swine vesicular disease, Newcastle disease, African swine fever, classical swine fever, *Brucella abortus*, vesicular stomatitis, and rabbit hemorrhagic disease or any other disease unless authorized by the Administrator
 - 5.4. The following statement shall appear on all labels: This is a prescription product. Use is subject to the discretion of the prescribing veterinarian.
 - 5.5. Distribution in each State shall be limited to authorized recipients designated by proper State officials—under such additional conditions as these authorities may require.
6. *Product Code*: A single product code for production platform-based prescription products is assigned by CVB. CVB will assign a unique product code for each licensed production platform system held by the licensed establishment.
7. *Release*: CVB will review APHIS Form 2008. Release for marketing will be granted without testing if the test results and sequence verification are satisfactory.