



Animal and Plant
Health Inspection
Service

Veterinary Services

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VETERINARY SERVICES MEMORANDUM NO. 800.214

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

FROM: for Jack A. Shere
Deputy Administrator

SUBJECT: Prescription Platform Product Biologics

I. PURPOSE

The Center for Veterinary Biologics (CVB) allows biologics manufacturers to use advanced technologies to license products manufactured with a standardized production platform (PP). Detailed guidance for platform products is provided in [Veterinary Services \(VS\) Memorandum Number \(No.\) 800.213](#). VS Memorandum No. 800.214 provides *additional* guidance to licensees, permittees, and applicants wishing to distribute customized (prescription) non-replicating, nonviable biological products using production platform-based technology. Unless specified otherwise in this memorandum, guidance in VS Memorandum No. 800.213 applies to prescription products as well.

II. BACKGROUND

The prescription platform product biologic (RxPP) is based on a written prescription from a veterinarian, for administration to animals within the context of a Veterinarian-Client-Patient Relationship (VCPR). Prescription platform biologics have no demonstrated claim of efficacy but are tested for safety and purity.

III. DEFINITIONS

A. Production platform (PP)

A production platform utilizes a single “backbone” vector or expression system (VES) and a standard process for inserting a gene(s) of interest (GOI) into the backbone to generate different recombinant Seeds or Sequences (constructs), which are then used to produce product following a standardized method for manufacture. The final product is non-replicating and nonviable. Refer to VS Memorandum No. 800.213.

B. Prescription Platform Product biologic (RxPP)

Custom veterinary biological product prepared for an individual animal or animals under a prescription written by a licensed veterinarian. Serials are manufactured based upon a licensed production platform.

C. Initial Product

A fully licensed biological product that establishes the product platform; the standardized method of manufacture; the maximum total antigen content; the permissible species for use, minimum animal age, dose, and route of administration (i.e., use specifications); and, safety for the RxPP. See [VS Memorandum 800.213](#) for additional detail regarding an Initial Product.

D. Total Antigenic Content

Total amount of antigenic material in a completed serial when the input of all fractions is combined. RxPP serials must not exceed the maximum total antigenic content defined in the Outline of Production. This establishes the upper limit for product safety.

E. Use specifications

The minimum age of the permissible species for use at the maximum total antigenic content per dose volume by a specific route of administration for the Initial Product.

F. Veterinarian-Client-Patient Relationship (VCPR)

VCPR is defined by title 9, *Code of Federal Regulations* (CFR), part 107.1 and the Principles of Veterinary Medical Ethics of the American Veterinary Medical Association. Prescribing veterinarians are responsible for ensuring a legitimate VCPR exists with the end user(s) of the RxPP.

IV. POLICY

A. Prerequisite for an Initial Product

The CVB will consider license applications for a RxPP once an Initial Product is fully licensed. Refer to VS Memorandum No. 800.213 for guidance on licensing an Initial Product. The CVB will not license a RxPP based on a conditionally licensed platform product.

B. Licensure of Prescription Product

The initial license for a RxPP will be granted upon approval of the first exchanged GOI of the Initial Product. The applicant must produce constructs for the GOI exchange with the identical VES, using the exact method documented in the Outline of Production for the Initial Product and without any changes to the manufacturing process. The completed product must have the same use specifications as the Initial Product.

C. Selection of GOIs

Under an RxPP license, the applicant may use constructs containing a variety of GOIs from different pathogens to manufacture serials for administration under the approved use specifications. This differs from nonprescription platform products, where the applicant may only substitute gene variants of the original GOI. The prescribing veterinarian may submit relevant microbial isolates or sequences from which the licensee or manufacturer will derive a GOI, or the prescribing veterinarian may select a GOI in consultation with the applicant.

To ensure that the use of RxPP biologics does not interfere with animal disease surveillance and control/eradication programs or pose other health risks, APHIS restricts the use of GOIs from certain microorganisms. The applicant must not produce RxPP serials from restricted organisms without authorization of the APHIS Administrator.

Currently, APHIS considers the following to be restricted:

- Diseases under Cooperative State/Federal/Industry Animal Disease Control and/or Eradication Programs, if APHIS determines that products may interfere with disease surveillance and/or control/eradication efforts.
- Diseases under the National List of Reportable Animal Diseases (NLRAD). See the [National Animal Health Reporting System \(NAHRS\) Reportable Disease List](#).
- Biological agents and toxins under the U.S. Federal Select Agent Program.
- Foreign Animal Diseases (FADs).
- Any other diseases/antigens not endemic to the United States in which products may endanger the animal agriculture of the United States.

D. Approval to Use New GOI

The CVB must approve each GOI used in an RxPP serial, and the GOI must be listed in the Outline of Production or Special Outline before the applicant manufactures a serial containing the GOI. The CVB expects applicants to consider and address each of the following aspects or points in their submissions for a request to begin manufacture of a new GOI:

- Field relevance of the GOI in the intended animal species. Include the geographic origin of the GOI and geographic location for product use.
- Potential safety impact of the new GOI when combined with the VES. Are there any characteristics resulting from this combination that might affect product safety in target and non-target animals?
- Inactivation method of the Initial Product. Is it reasonable to expect that the same method will be sufficient for this construct? What would be the impact if the expression product of the GOI was not fully inactivated by the current method? Conversely, could the immunogenicity of the expression product (e.g., a toxin) be adversely impacted by the current inactivation method?
- Public health safety considerations for the GOI.
- The CVB may require the applicant to provide additional studies and to perform confirmatory testing on potential new constructs prior to filing the Outline of Production or Special Outline.

E. Manufacturing

The applicant must make all constructs in facilities located within the United States or any place under the regulatory jurisdiction of the United States. Refer to VS Memorandum No. 800.213 for additional information.

The CVB allows split manufacturing, based on the established manufacturing of the Initial Product, but the CVB does not allow sublicensure to another Establishment. See VS Memorandum No. 800.213 for details.

The CVB handles requests to make changes in manufacturing of a licensed RxPP, as described in VS Memorandum No. 800.213. The CVB must evaluate any change to the standardized method of manufacture, regardless of perceived impact, prior to incorporation of the change. Material or manufacturing changes may require the establishment of a new Initial Product and, subsequently, a new RxPP license.

F. Changes to Use Specifications

The CVB requires supporting field safety studies if there is a change in any of the use specifications of a licensed RxPP. The applicant must submit a proposal stating the intended modification, an updated Category IV Summary Information Format, and a field safety study protocol for approval prior to conducting the study.

G. Creating Multi-Valent Serials

The CVB determines the number of GOIs allowable in one construct based on the construct approved by the CVB for use in the Initial Product. The CVB allows the number of GOIs in an individual serial to be increased by creating product fractions, each fraction containing a different GOI. The CVB restricts the allowable fractions in a serial by the maximum total antigenic content for which safety has been demonstrated.

H. Testing

The Outline of Production must contain at least the following, so that product consistency can be evaluated:

1. **Batching consistency method.** An objective in-process, per-dose measure of the amount of a single construct harvest (fraction) blended into a serial. Describe the method(s) in section IV. Cite the section IV testing in section V and include results on the APHIS Form 2008 to fulfill serial release requirements.
2. **Analytical quantification method.** This determines total antigenic content in the completed serial and is intended to ensure the serial contains no more antigen than has been demonstrated safe. The applicant must describe this test method, with applicable validation criteria, in section V.C. Examples of possible assay methods include, but are not limited to, immunoassays, liquid chromatography, and total protein analysis.
3. **Identity testing.** This confirms the completed serial contains the correct construct(s). The applicant must provide an identity test for each fraction. Depending on the nature of the product, the identity test may be conducted on completed product or on the bulk antigen. Describe the method(s), with applicable validation criteria, in section V.E. and include results on the APHIS Form 2008 to fulfill serial release requirements.
4. **Final product testing for sterility and safety (9 CFR 113.100(a) and (b)).** The CVB requires testing as established by the Initial Product.

I. Product Dating

Applicants should propose and justify an appropriate means for establishing serial expiration dating, based on the manufacture date of the earliest bulk harvest of the GOI and the storage conditions for that bulk. The CVB will evaluate the proposal and set product dating accordingly.

J. Serial and Sample Submission/Retention

Veterinary Biological Product Samples are selected, authenticated, and submitted according to 9 CFR 113.3 and VS Memorandum No. 800.59.

Based on the number of containers produced, the licensee should allocate samples as follows:

1. For serials with <50 containers, the licensee selects 2 government reserve samples only.
2. For serials with ≥ 50 containers, the licensee selects 10 government submission samples but is only required to submit 2 samples. After the serial has been released to the market, the licensee may return 6 samples to salable inventory and maintain 2 government reserve samples.

K. Outlines of Production

The applicant must include the following in the designated sections of the Outline of Production for an RxPP:

1. General. All information as required for platform products per VS Memorandum No. 800.213 and VS Memorandum No. 800.206; methods must match the methods described in the Outline for the Initial Product.
2. Section I. The method(s) for determining the identity of a submitted isolate or sequence from which a GOI will be obtained, and a detailed description of how each GOI is introduced into the VES and subsequent testing to confirm purity and identity.
3. Section IV.I. State the maximum permissible total antigenic content.
4. Section V. Information for product testing, as stated in section IV.H of this memorandum.
5. Section VI.B. Information on serial sampling per section IV.J of this memorandum.

L. Serial Release

The CVB allows release in accordance with 9 CFR 113.3, 113.6, and 116.7, with additional guidance listed in VS Memorandum No. 800.53, Release of Biological Products.

The applicant must report the following *additional* information on the APHIS Form 2008:

1. The identity (licensee's internal identification) of each GOI in the serial.
2. Biological agent of each GOI.
3. Date of Manufacture for each GOI bulk in the serial (to determine expiry dating).
4. Host animal species and route of administration for which the product is intended.

M. Labels

Applicants must prepare labels according to 9 CFR 112 and VS Memorandum No. 800.54.

The applicant must structure labels as required for conditional licensed products; however, the claim statement must include the following: "For vaccination against the organisms and strains listed. This product is a prescription platform veterinary biologic to be used under the supervision of a licensed veterinarian. Efficacy and potency have not been demonstrated."

N. Packaging

Licensees must package RxPPs consistent with requirements for other licensed products. All vaccine fractions must be packaged in a single container; however, diluent or adjuvant may be provided in a separate container. Refer to VS Memorandum No. 800.74 for information regarding sterile diluents.

O. Marketing and Promotional Materials

The CVB limits product advertising and marketing to notification of availability of prescription platform product biologics. The CVB does not permit advertising that compares products, or infers or claims efficacy or potency. The CVB must review all promotional and advertising materials prior to publication or distribution.

P. License Restrictions

The CVB issues RxPP licenses with several restrictions. The restrictions will read:

- This license will expire in 2 years. The license may be renewed upon request by the firm and at the discretion of APHIS based on manufacturing consistency and inspections by the Center for Veterinary Biologics. For use by veterinary prescription by and under the supervision of a licensed veterinarian.
- Trade names shall not be used with this product.
- Marketing and promotional materials must be reviewed by the CVB prior to publication or distribution.
- Distribution in each State shall be limited to authorized recipients designated by proper State officials—under such additional conditions as these authorities may require.
- Export distribution shall be limited to authorized recipients designated by proper animal health regulatory officials—under such additional conditions as these authorities may require.
- This license does not authorize production, distribution, or shipment of a vaccine/bacterin 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 that the Administrator determines may pose a risk to animal or public health.
- Unusual conditions or adverse events linked to vaccinated animals are to be reported to the CVB quarterly.
- Disposition records, maintained according to 9 CFR 116.2, shall be prepared in a format acceptable to APHIS and submitted to the CVB at intervals determined by APHIS.

With regard to the final restriction listed above, licensees must submit a report to the CVB quarterly including the number of doses produced and destroyed for each serial, and indicating GOI and animal species for use.

V. IMPLEMENTATION/APPLICABILITY

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

This policy is effective immediately.