Veterinary Services
Safeguarding Animal Health

Animal and Plant Health Inspection Service

Veterinary Services

Center for Veterinary Biologics

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Shipping Experimental Product

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Notes:

Production and Shipment of Experimental Veterinary Biological Products and Related Issues

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Introduction

Production and distribution of experimental veterinary biological products are regulated by title 9, *Code of Federal Regulations* (9 CFR), section 103, as is the disposition of animals that have been administered experimental products.

The CVB considers experimental product to include Master Seeds and Master Cells, and any product or intermediate derived from them, excluding licensed product. Unlicensed diagnostic test kits are considered experimental product.

Production of Experimental Product in Licensed Facilities

Production of experimental product on licensed premises is regulated in 9 CFR 103.1.

When experimental product is produced in a licensed facility, it is best if it can be done in a research facility that is separate and apart from production facilities. In many small firms, however, there is no clear separation between research and production. It is permissible to prepare experimental products that contain only previously approved seeds and cells in production facilities. If a firm wishes to use unapproved seeds or cells in production facilities (or research facilities that are not separate and apart), however, the firm must request permission from the CVB-PEL; guidance regarding such requests is found in Veterinary Services Memorandum 800.64.

[redacted]

Shipment of Experimental Product Intended for Use in Animals

Persons wishing to ship an unlicensed biological product for experimental use *in animals* must request permission from the CVB, per 9 CFR 103.3. This includes shipment of unlicensed product for use in host animals (field efficacy or safety trials), as well as some instances of use of unlicensed product in laboratory animals. The following table lists the most common shipment scenarios that require 103.3 authorization or permission from the CVB:

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Require 103.3	[redacted]
Master Seeds/Cells and anything derived from Master Seeds/Cells that will be used in animals. This includes any purpose from field trials to the generation of sera.	[redacted]
Shipment of experimental product between independently owned Establishments if the material will be used in animals.	[redacted]
Shipment of prelicense FFM if the material will be used in animals.	[redacted]
Shipment of prelicense diagnostic test kits.	
Shipment of unreleased licensed product between independently owned Establishments if the product will be used in animals.	[redacted]
Shipment of licensed product for off-label use if there are license restrictions.	[redacted]
Shipment of any of the above materials to ARS or other government agencies, except for materials shipped to the CVB for confirmatory testing.	[redacted]
Require permission from CVB, but do not require 103.3	
Shipment of materials between independently owned Establishments if the material will not be used in animals.	[redacted]
Shipment of prelicense FFM if the material will not be used in animals.	
Shipment of unreleased licensed product between independently owned Establishments if the product will not be used in animals.	[redacted]
Shipment of licensed product for off-label use if there are no license restrictions; the firm must provide permission from the State Veterinarian for the off-label use.	[redacted]
Do not require permission from CVB or 103.3	
Master Seeds/Cells and anything derived from Master Seeds/Cells that will not be used in animals. Notification of shipment is recommended, particularly for select agents and high profile antigens.	[redacted]
Materials to be used for hybridoma development in laboratory rodents. Notification of shipment is recommended, particularly for select agents and high profile antigens.	[redacted]
Shipment of materials between different sites of the same Establishment.	[redacted]

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Shipment of materials between two Establishments that are under the same ownership. [redacted]	[redacted]
Shipment of DEREA products overseas prior to CVB acknowledgement of foreign marketing authorization [redacted]	[redacted]
Shipment of challenge organisms.	
Miscellaneous	
Authorization under 103.2 is required for movement of vaccinated animals prior to 14 days postvaccination (or after 14 days postvaccination if there is a concern regarding shedding or slaughter withdrawal).	[redacted]
A copy of the recipient's IBC approval must be submitted for shipments of recombinant materials prior to the issuance of a FONSI. Refer to CVB Notice No. 07-06.	[redacted]
Blanket 103.3 approvals for specific products, specific recipients, and a specified time period can be granted upon the reviewer's discretion. The firm's request must meet all requirements of 103.3 [redacted]	[redacted]

Additional guidance is found in Veterinary Services Memorandum 800.67. This regulation does not apply to experimental product shipped between licensed premises of a single establishment for use on licensed premises, nor does it apply to product shipped for *in vitro* evaluation (e.g., laboratory analysis). In general, 103.3 authorization is required to ship unreleased serials manufactured in production to sites that are not listed on the establishment license, for use in animals. General Department of Transportation shipping regulations (e.g., hazardous goods, select agents), however, apply to all shipments, regardless of destination or intended use.

Any exceptions to these generalizations should be approved by PEL, documented with a letter to the firm, and kept on file.

[redacted]

A request for authorization to ship an unlicensed biological product for experimental study must be accompanied by the following:

1. Letter of authorization, from the proper State or foreign animal health authority, to conduct experimental studies in that State/country. Multi-site studies require permission from each participating State/country.

The proper State animal health authority usually is the State Veterinarian. Occasionally the State's animal health authority is not a veterinarian, but is a designated commissioner.

Some state authorities do not issue authorization letters, responding instead that they have no statutory authority to either approve or disapprove these studies. The CVB's position on these "neutral" responses is that the state was given the opportunity to take a position. In the absence of a state disapproval, reviewers may authorize shipment if the documentation presented to the CVB is otherwise acceptable.

2. Tentative list of proposed recipients (study participants) and the quantity of product to be shipped to each recipient. If this list changes, an update must be submitted. The number of doses should be reasonable for the study objective. Studies proposing thousands of animals for poorly defined objectives (or objectives not directly related to meeting licensing requirements) are generally not acceptable. Authorization to ship under 9 CFR 103.3 should not be used as a mechanism to gain early market exposure for products.

3. A description of the product (or Outline of Production, if available), including the serial number(s). It should include recommendations for use (often found on a label sketch) and results of preliminary research (if available).

4. Test results for each serial to be shipped. Each serial must have tested satisfactorily for purity, safety, and any other tests required by the CVB.

5. Label sketches, which show the true name of the product and bear a statement "Notice! For Experimental Use Only-Not For Sale" or equivalent. (Ensure that alternate syntax truly is equivalent.) The U.S. Veterinary License No. must not appear on experimental labels.

6. A study protocol, including methods and procedures.

7. If the product is intended for parenteral use in food animals, the firm must submit data demonstrating that use of the product will not result in adulterated meat/poultry/fish. The firm should also provide a statement from the research investigator(s) that they will provide, upon our request, information concerning all food animals involved prior to movement of these animals from the study premises.

Reviewing 103.3 Requests

The reviewer must ensure that all of the requirements for shipment, listed above, are met. Additionally, he/she must determine if the provisions of the National Environmental Policy Act (NEPA) of 1969 (42 U.S.C. 4371) are triggered. Provisions of NEPA are triggered whenever there is a proposed Federal action with a potential impact upon the environment. APHIS approval to release an experimental veterinary biological product into the environment can be such a Federal action.

Theoretically, any experimental veterinary biologic may trigger NEPA. In current practice, however, the CVB performs environmental assessments (EA) only on Category II (live microorganisms that contain gene deletions and/or heterologous marker genes) and Category III (live expression vectors that contain heterologous genes) recombinant products. Additional categories (e.g., GMO plants producing veterinary biological products) will likely be added in the future. In such cases, a firm must submit the appropriate Summary Information Format (see SIF chapter in Reviewer's Manual) and environmental assessments (EAs). See Veterinary Services Memoranda 800.50 and 800.205 for additional guidance on SIFs and EAs. Shipment of experimental product is authorized only after a conclusion of No Significant Impact is found on environmental risk assessment.

If the 103.3 request is made by submission of APHIS Form 2071, Application for Authorization to Ship Experimental Veterinary Biological Product, the reviewer only needs to sign the bottom of the form, if all supporting materials are included and are satisfactory [redacted]

Upon approval of the request, a response letter is prepared, if the incoming submission came by a letter, and not using APHIS Form 2071. See the example letter in Appendix I of this chapter. Response letters should include the following:

1. Standard opening text (date of submission, true name of product, product code)

2. Serial(s) to be shipped

3. Name(s) of authorized recipients and quantity of product to be shipped.

4. Type of study being performed.

5. Acknowledgement of receipt of written permission from proper state regulatory officials where field trial is to be conducted.

6. Acknowledgement of protocol. Provide comments on the protocol, as applicable, if they have not been addressed under separate cover.

7. Citation of applicable regulation (9 CFR 103.3)

8. Statement that firm must comply with additional State regulations, if applicable.

9. Time limit for authorization (1 year is typical). Also include a reminder that extensions, if needed, must be formally requested.

10. Reminder that results of the study must be reported to the CVB

11. Enclose a "date-stamped" copy of the experimental label. Experimental labels are [redacted] stamped with a date and returned to the firm for their files.

[redacted]

[redacted]

[redacted]

[redacted]

Filing 9 CFR 103.3 authorizations for uncoded products

Often, permission is requested to ship products for preliminary discovery (proof-of-concept) studies. These products have not yet progressed to the point where the firm is proposing them for licensure; thus, they do not have a product code assigned to them. Uncoded correspondence such as this would ordinarily be filed as Code NA0000, but such items are subject to archival each year. If Reviewers do not want authorizations to ship experimental product to be archived annually because some of these products will eventually be proposed for licensure, they must either remove the 103.3 designation from the portal entry OR place the item into a licensing plan. Also, the original request should remain in the active files to ensure that the summary report is submitted.

All authorizations for coded products are filed under the Product Code for that product.

Requests to ship licensed products for off-label use or for purposes outside of established product license restrictions

Firms will frequently submit requests to ship licensed product for off-label use or for purposes outside of the product license restrictions.

Examples:

- To ship a licensed vaccine currently labeled for dogs to be used in a ferret efficacy study intended to expand label claims
- To ship a licensed vaccine, restricted to use in state and federal regulatory programs, to a foreign country for use in their government-authorized study

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Reviewers should write an authorization letter in regard to all requests for field studies conducted by off-label use. The documents that the firm must submit to support the request, however, can vary.

Technically, if a firm is shipping a licensed serial that IC has released AND if the containers are labeled with a CVB-approved label (their usual market label), the firm does not need authorization under 9 CFR 103.3 to ship it. Nonetheless, the firm will be directing the study cooperators to use the product off-label. While we cannot regulate voluntary off-label use by end-users, we do not allow firms to endorse off-label use of their products themselves. For this reason, a protocol and a letter from the state vet, indicating that they will allow the off-label study, should be submitted. Other documents associated with a 103.3 request are probably not necessary in such a situation.

The CVB response letter should authorize the off-label study, but does not need to say that it is authorized "under 103.3". If the containers are to be labeled with an experimental label instead of the approved market label, then an experimental label needs to be submitted in addition to the protocol and state vet letter. Additional documentation may be required, at the reviewer's discretion, for other case scenarios.

When shipping a licensed, released serial for an off-label use authorized by a government authority like Wildlife Services (WS), a notification letter to CVB should be submitted but documents including authorization by the State Regulatory Authority, or a protocol are usually not necessary. NEPA requires risk assessments, Federal Registrar notices, FONSIs, etc for products to be introduced into the wilderness or wildlife populations and WS ensures compliance with these requirements.

Extreme deviations from usual product use may cross the line into 103.3 (Example: using a product in a manner that is outside the use restrictions placed on the product license). For those, all of the requirements for 103.3 submissions apply.

<u>Shipping and Disposition of animals that have received experimental products</u>

9 CFR 103.2 prohibits animals from leaving study premises for at least 14 days after administration of the experimental product or live organisms (vaccination or challenge). The 14-day holding period may be increased or decreased by APHIS following review of relevant data. Criteria described in 9 CFR 103.3 may be required for animals vaccinated for high visibility/politically sensitive diseases (for example birds vaccinated for avian influenza, or cattle vaccinated with a synthetic Foot and Mouth Disease product).

Food animals may be sent to slaughter provided they meet the conditions described in the 9 CFR 103.2 and are accompanied by a Slaughter Permit issued by the Food Safety Inspection Service. A slaughter permit is not required if the study is conducted after a slaughter withdrawal period for the product has been approved by the CVB and the animals are held for that period prior to slaughter.

Regarding dairy cattle vaccinated with experimental product, vaccines are exempt from Pasteurized Milk Ordinance (PMO) labeling requirements. Local state officials must still be notified, however, if milk from dairy cattle vaccinated with experimental vaccine is to be sold for human consumption. The CVB should advise the firm to notify appropriate state officials.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Follow-up on experimental studies

At the conclusion of studies using product shipped under 9 CFR 103.3, firms must submit results to the CVB. At a minimum, results must be summarized, but if the studies are pivotal to licensure, complete reports should be submitted. Results are expected within the prescribed timeframe (usually one year) determined by the CVB. [redacted]

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