U.S. Department
of Transportation

Pipeline and Hazardous
Materials Safety
Administration

1200 New Jersey Avenue, SE
Washington, DC 20590

MAR 20 2018

Mr. Jon Harrington
Director of Manufacturing Operations
Vyriad
221 1st Avenue SW, Suite 102
Rochester, MN 55902

Reference No. 17-0076

Dear Mr. Harrington:

This letter is in response to your July 24, 2017, email requesting clarification of the Hazardous Materials Regulations (HMR; 49 CFR Parts 171-180) applicable to infectious substances. Specifically, you currently offer for transportation two live viruses: 1) Vesicular stomatitis virus (Indiana), or VSV, as a Category A infectious substance, and 2) Measles, as a Category B infectious substance. You ask if the HMR provide any exceptions for biological products as defined in § 173.134(a)(2), and if so, whether they may be used for live viruses stored for manufacturing purposes.

The answer to both of your questions is yes. As prescribed in § 173.134(b)(6), a biological product, including an experimental or investigational product or component of a product, subject to Federal approval, permit, review, or licensing requirements, such as those required by the Food and Drug Administration of the U.S. Department of Health and Human Services or the U.S. Department of Agriculture Animal and Plant Health Inspection Service (APHIS), is not subject to the requirements of the HMR as a Division 6.2 material.

Since APHIS granted you a permit to import and transport the VSV, it is not subject to the requirements of the HMR as a Division 6.2 material. However, because the Measles virus is not subject to another Federal approval, permit, review, or licensing requirement, it is subject to the HMR as a Division 6.2 material, and as a Category B infectious substance, it must be described as "Biological substance, Category B" and assigned identification number "UN3373" for transportation in commerce. Live viruses stored for manufacturing purposes are also eligible for the exceptions provided by § 173.134 of the HMR.

I hope this information is helpful. Please contact us if we can be of further assistance.

Sincerely,

T. Glenn Foster
Chief, Regulatory Review and Reinvention Branch
Standards and Rulemaking Division

Stevens
§173.134
Definitions
17-0076

Dodd, Alice (PHMSA)

From: INFOCNTR (PHMSA)
Sent: Tuesday, July 25, 2017 4:29 PM
To: Hazmat Interps
Subject: FW: clarification for shipping
Attachments: 2017-05-04_600390_Permit_Cover_TO.pdf

Hi Alice,

Please submit this as a letter of interpretation. Mr. Harrington spoke with Breanna. Please let me know if you have any questions.

Thanks,
Jodi

From: Jon Harrington [mailto:jharrington@vyriad.com]
Sent: Monday, July 24, 2017 4:13 PM
To: INFOCNTR (PHMSA) <INFOCNTR.INFOCNTR@dot.gov>
Subject: clarification for shipping

Requesting a formal letter of interp.

Dear DOT,

This is a repeat message. I wanted to add a read receipt to make sure you received the information.

I am looking for some clarification for the shipping of two biological products.

Vyriad is conduction clinical trials using two different types of viruses for treating cancer.

1. Measles: MV-NIS
   MV-NIS is a live, tissue culture adapted measles virus engineered to express the human thyroidal sodium iodide symporter (NIS). The virus was constructed by inserting the NIS gene (cDNA) into a
   full - length infectious molecular clone of an attenuated Edmonston lineage measles virus (MV-tag).
   This virus is not a vaccine. MV-NIS propagates on Vero cells with kinetics equivalent to the parental
   strain of virus. It propagates selectively in human cancer cells that it infects by binding preferentially to
   CD46, a membrane protein that is overexpressed in tumor cell lines. The virus is directly cytopathic to
   tumor cells leading to the formation of multinucleated syncytia that die by apoptosis. MV-NIS infected

tumor cells express NIS, a membrane ion channel that actively transports iodide into cells. Radioiodine
uptake by cells expressing NIS provides the basis for in vivo radioiodine imaging that can reveal the
profile of MV-NIS gene expression and the location of MV-NIS infected cells during virus spread and
elimination.

2. VSV(Vesicular stomatitis virus): VSV-IFN β -NIS
VSV-IFN β-NIS is a live virus engineered to express both the human interferon β gene and the thyroidal
sodium iodide symporter (NIS). The virus was constructed by inserting the gene for human IFN β
downstream of M gene and the NIS gene (cDNA) downstream of the gene for the G protein into a full-
length infectious molecular clone of an Indiana strain VSV. This virus is not a vaccine. VSV-IFN β -NIS
propagates on BHK cells with similar kinetics to the parental strain of virus and can be grown to high
titers. It propagates selectively in human cancer cells since many of them cannot mount an effective
antiviral response mediated via the IFN pathway. However, IFN production from infected cells will
serve to protect non-cancer cells from the effects of the virus. As a result, the virus is directly cytopathic to tumor cells leading their rapid lysis with amplification of the virus. VSV-IFN β -NIS infected tumor cells also express NIS, a membrane ion channel that actively transports iodide into cells.
Radioiodine uptake by cells expressing NIS provides the basis for in vivo imaging with 99mTc pertechnetate or radioiodine I-123 that can reveal the time dependent profile of VSV-IFN β -NIS gene expression and the location of VSV-IFN β -NIS infected cells during virus spread and elimination.

Currently we are shipping 2mL dosages to clinical trials sites using Category B requirements for the measles virus and Category A requirements for the VSV. Vyriad is required to make sure clinical trial sites have a permit for receipt of VSV material through Aphis (see attached). Using Category A and B shipping containers are a very costly method of shipping for a startup company like ours and would like to explore alternatives if possible. Does this material qualify as an exception §173.134? If the material qualifies for an exemption, what classification can we use to ship the materials?

Additionally, we have measles and VSV materials stored for manufacturing purposes. Can we ship this material under the same exemption?

I appreciate your time and consideration. How long does the evaluation process normally take? I would like to relay the approximate timeline to my CEO.

Kindest Regards,
Jon Harrington
Director of Manufacturing Operations

VYRIAD

221 1st Ave SW, Suite 102, Rochester, MN 55902
O: 507.722.0231 | M: 608.698.5331 | jharrington@vyriad.com | www.vyriad.com

United States Department of Agriculture

Animal and Plant Health Inspection Service

Veterinary Services

National Center for Import and Export

4700 River Road
Unit 2, Mailstop 22,
Cub. 1A07
Riverdale, MD 20737

(301) 851-3300
FAX (301) 851-2239

Jonathan Harrington
Vyriad
221 1st Ave. SW, Suite 102
Rochester, MN 55902

Thursday, May 4, 2017

Dear Jonathan Harrington:

Your USDA Veterinary Permit 133771 to import and/or transport controlled materials, organisms and vectors accompanies this cover letter.

Your USDA Veterinary Permit to import and/or transport controlled materials, organisms, or vectors accompanies this cover letter.

Review this permit carefully, as the statements and language may have changed to reflect the requirements of newly published regulations.

Please note the following:

- Review the import permit for errors. Should you identify any errors, please contact our office immediately
- A copy of the permit must accompany every shipment.

Do Not send the permit back to this office.

USDA Veterinary Permits no longer require a signature. Use of the permit for importation of the described commodity(ies) is acknowledgement that the permittee is legally responsible for complying with the permit conditions.

For frequently asked questions, permit process and updates, visit: www.aphis.usda.gov/animal-health/organisms-vectors . Contact our office with any questions or concerns by email at: ov@aphis.usda.gov or telephone at 301-851-3300, option 3.

Sincerely,

Dr. Troy Bigelow
Senior Staff Officer
Organisms and Vectors, and Select Agents
National Import Export Services

re: application number 17095116

U.S.DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE
VETERINARY SERVICES
RIVERDALE, MARYLAND 20737
file:///D:/Inetpub/wwwroot/Epermits/images/

UNITED STATES VETERINARY PERMIT FOR IMPORTATION AND TRANSPORTATION OF CONTROLLED MATERIALS AND ORGANISMS AND VECTORS

PERMIT NUMBER
133771
Research

DATE ISSUED
05/04/2017

DATE EXPIRES
05/04/2018

NAME AND ADDRESS OF SHIPPER(S)

Jon Harrington
Vyriad
221 1st Avenue SW, Suite 102
Rochester, Minnesota 55902
UNITED STATES

CC:
Service Center, MN (St. Paul, MN)
CVB-LPD (Ames, IA)
FDA (Rockville, MD)

NAME AND ADDRESS OF PERMITTEE INCLUDING ZIP CODE AND TELEPHONE NUMBER

Jonathan Harrington
Vyriad
221 1st Ave. SW, Suite 102
Rochester, Minnesota 55902
507-289-0944 / 608-698-5331

U.S. PORT(S) OF ARRIVAL
TRANSPORT PERMIT

MODE OF TRANSPORTATION ANY

AS REQUESTED IN YOUR APPLICATION, YOU ARE AUTHORIZED TO IMPORT OR TRANSPORT THE FOLLOWING MATERIALS

Recombinant oncolytic Vesicular stomatitis virus (Indiana) - Purified, vialled tissue culture-derived virus preparations of recombinant VSV-IFNb-NIS

RESTRICTIONS AND PRECAUTIONS FOR TRANSPORTING AND HANDLING MATERIALS AND ALL DERIVATIVES

THIS PERMIT IS ISSUED UNDER AUTHORITY CONTAINED IN 9 CFR CHAPTER 1, PARTS 94,95 AND 122. THE AUTHORIZED MATERIALS OR THEIR DERIVATIVES SHALL BE USED ONLY IN ACCORDANCE WITH THE RESTRICTIONS AND PRECAUTIONS SPECIFIED BELOW (ALTERATIONS OF RESTRICTIONS CAN BE MADE ONLY WHEN AUTHORIZED BY USDA, APHIS, VS).

- **Adequate safety precautions shall be maintained during shipment and handling to prevent dissemination of disease.**

- With the use of this permit I, Jonathan Harrington, Permittee, acknowledge that the regulated material(s) will be imported/transported within the United States in accordance with the terms and conditions as are specified in the permit. The Permittee is the legal importer/recipient [as applicable] of regulated article(s) and is responsible for complying with the permit conditions. The Permittee must be at least 18 years of age and have and maintain an address in the United States that is specified on the permit; or if another legal entity, maintain an address or business office in the United States with a designated individual for service of process; and serve as the contact for the purpose of communications associated with the import, transit, or transport of the regulated article(s). **Note: Import/Permit requirements are subject to change at any time during the duration of this permit.

- ***Materials shall be consigned directly to the permittee address specified above.

continued on subsequent page(s).....

TO EXPEDITE CLEARANCES AT THE PORT OF ENTRY, BILL OF LADING, AIRBILL OR OTHER DOCUMENTS ACCOMPANYING THE SHIPMENT SHALL BEAR THE PERMIT NUMBER

SIGNATURE	TITLE	NO. LABELS
Troy Bigelow	Senior Staff Veterinarian National Import Export Services	

RESTRICTIONS AND PRECAUTIONS: (continued from Permit Form VS 16-6)

- Work shall be limited only to laboratory studies and or human clinical trials. This permit does NOT authorize direct or indirect exposure of or inoculation into domestic or laboratory livestock (including but not limited to: birds/poultry/eggs, cattle, sheep, goats, swine, and horses). This permit DOES authorize direct and indirect exposure of and inoculation into other animal species and for human clinical trials. All exposed animals must be held only in isolated facilities with insect and rodent control program in effect.

- Packaging, containers, and all equipment in contact with the imported products shall be sterilized or considered a biohazard and must be disposed of accordingly.

- Pens, cages, bedding, waste, and dead animals in contact with these materials shall be sterilized or considered a biohazard and be disposed of accordingly.

- This permit authorizes the transport of this material into your research and development facilities. Introduction of this material into the production areas of your USDA, APHIS, licensed establishment must be approved by the Center for Veterinary Biologics (CVB). Storage locations, movements, and use within your licensed premises must be reported to CVB.

- Imported material, clinical trials and animal trials may be subject to regulations enforced by the United States Food and Drug Administration (FDA). Importer must contact the Division of Import Operations and Policy at Area Code (301) 796-0356.

- THIS PERMIT IS VALID ONLY FOR WORK CONDUCTED OR DIRECTED BY YOU OR YOUR DESIGNEE IN YOUR PRESENT U.S. FACILITY OR APPROPRIATELY INSPECTED LABORATORY. THE AUTHORIZED IMPORTED MATERIAL(S) MUST BE SHIPPED/CONSIGNED DIRECTLY TO THE ADDRESS OF THE PERMITTEE OR TO THE ADDRESS OF THE ADDITIONAL PERMITTEE(S) AS IDENTIFIED ON THIS PERMIT. (MATERIALS SHALL NOT BE MOVED TO ANOTHER U.S. LOCATION, OR DISTRIBUTED WITHIN THE U.S., WITHOUT USDA, APHIS, VS, NIES AUTHORIZATION.) ++EXCEPTION++ Material is authorized to be distributed to human clinical trial sites, animal testing sites, and biorepository, but Jonathan Harrington, Vyriad, retains responsibility for compliance to the permit. Locations shall be recorded and made available to the USDA upon request.

- This permit only authorizes exposure to animals for trials associated with development of a human product per direction and guidance of the FDA. Documentation from FDA on FDA animal trial requirements must be available to the USDA upon request. Animal trials of any type for development of an animal product, animal related vaccine or derivative thereof are not authorized. Contact the Center of Veterinary Biologics for information regarding development of animal vaccines or products.

- This permit does not exempt the permittee from responsibility for compliance with any other applicable federal, state, or local laws and regulations.

- A copy of this permit must be included with the shipping documents.