U.S. Department
of Transportation

Pipeline and Hazardous Materials
Safety Administration

1200 New Jersey Ave., SE
Washington, DC 20590

SEP -4 2009

Ms. Debra A. Brickey, PhD
Responsible Official Select Agent Program,
Central and Waterfront Campuses
Oregon Health and Science University, PP-170
3181 SW Sam Jackson Pk Rd
Portland, OR 97239-3098

Ref. No. 09-0186

Dear Dr. Brickey:

This responds to your June 31, 2009 email requesting an interpretation of the applicability of the Hazardous Materials Regulations (HMR; 49 CFR Parts 171-180) to the transport of Division 6.2 materials. Specifically, you ask whether mice infected with a replication defective adeno-associated virus (AAV) are subject to the requirements of the HMR.

The information attached to your email indicates that the mice are infected with a type of AAV that does not cause disease in humans or animals. The AAV injected into the mice is inactivated such that it does not replicate itself in the host; thus, the mice do not contain infectious AAV viral particles.

Under § 173.134, a Division 6.2 Infectious substance is defined as a material known to contain or reasonably expected to contain a pathogen, such as a virus, that can cause disease in humans or animals. Additionally, under exceptions provided in § 173.134(b), a material containing pathogens that have been neutralized or inactivated such that they no longer pose a health risk is not subject to the requirements of the HMR as a Division 6.2 material. Based on the information provided in your email, it is the opinion of this Office that the mice do not meet the definition of a Division 6.2 material and are not subject to the HMR.

I hope this information is helpful. If you have further questions, please contact this office.

Sincerely,

Charles E. Betts
Chief, Standards Development
Office of Hazardous Materials Standards

Der Kinderen
§172.101
Applicability
09-0186

Drakeford, Carolyn (PHMSA)

From: Gorsky, Susan (PHMSA)
Sent: Friday, August 07, 2009 3:00 PM
To: Drakeford, Carolyn (PHMSA)
Cc: Lavalle, Diane (PHMSA); Mazzullo, Ed (PHMSA)
Subject: FW: OHSU Animal shipment to Germany

From: Debra Brickey [mailto:brickeyd@ohsu.edu]
Sent: Friday, August 07, 2009 2:35 PM
To: Special Permits (PHMSA)
Cc: Sally Finch; Kim Saunders; John Brigande; Gwynn Daniels
Subject: RE: OHSU Animal shipment to Germany

Hi Diane,

Thank you for your assistance. I talked this over with the OSHU director of the Department of Comparative Medicine and we both agreed that at these animals would not have any non-integrated replication-incompetent adeno-associated virus. These mice would not pose a hazard to humans or other animals due to the procedure done to them as embryos.

If you could provide us with an email approval and a written approval so that we may ship as soon as animals are ready, it would be very appreciated by all of us here at OHSU.

Debra

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From: specialpermits@dot.gov [mailto:specialpermits@dot.gov]
Sent: Friday, August 07, 2009 7:01 AM
To: Debra Brickey
Cc: Kenneth.Herzog@dot.gov; Darral.Relerford@dot.gov
Subject: RE: OHSU Animal shipment to Germany

Hi Debra,
Your email indicates the mice are not pathogenic to other mice, rodents, or humans. We need to be sure the mice are not pathogenic to animals other than rodents. If you can assure us that the mice are not pathogenic to humans or animals, then we would agree they are not regulated as Division 6.2 materials under

the HMR.
We can respond by email immediately, a written response will take a bit.
Thanks,
Diane LaValle
Transportation Specialist

From: Debra Brickey [mailto:brickeyd@ohsu.edu]
Sent: Thursday, August 06, 2009 3:23 PM
To: Special Permits (PHMSA)
Subject: FW: OHSU Animal shipment to Germany
Importance: High

To the attention of Darrell Releford. This in reference to the permit for Oregon Health & Science University (OHSU) to ship mice from the US to Germany on passenger aircraft.

From: Debra Brickey
Sent: Friday, July 31, 2009 10:45 AM
To: 'kenneth.herzog@DOT.gov'
Subject: OHSU Animal shipment to Germany
Importance: High

Kenny,

Here is Dr. John Brigande's explanation of his virus work in these mice. What it boils down to is that the virus Is not in the mice at the time of shipping. The genes carried by the virus are in the mice but all of the virus has been eliminated by the mouse cells. The delays have lead to a minimum cost of $6000 dollars to the lab due to the age requirement for the mice needed for the experiment an expedited assessment would be greatly appreciated by all those involved in the permit process at OHSU and Germany.

If based on this you decide that a permit is not required, could you give us a written declaration of this assessment? Do you think we could have resolution on this by early next week?

Thanks,

Debra

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From: John Brigande
Sent: Thursday, July 30, 2009 8:34 PM
To: Debra Brickey; Sally Finch
Cc: Chris Bresee

Subject: RE: Animal shipment to Germany

Deb,

The wild type adeno-associated virus (AAV) is a member of the parvovirus family that displays no pathogenicity in humans. The virus is composed of a single stranded DNA genome that comes in two versions: sense or coding and anti-sense or non-coding. The wild type virus in humans can integrate into a specific site called AAVS1 in human chromosome 19. Because it is not associated with any pathogenic or disease state in humans and because it does integrate, AAV has been developed as a gene therapy vector for use in treating human diseases through gene replacement. Currently, there are clinical trials using AAV-based vectors for gene therapy for lipid storage disease; muscular dystrophy; and Canavan disease. Completed human clinical trials using AAV-based gene therapy vectors have focused on cystic fibrosis, arthritis, and hereditary emphysema among other diseases.

The vector we are working with is a replication defective version of the non-pathogenic wild type virus. Our virus is also non-pathogenic, and it does not make more of itself in the infected host. The genome of our virus has deletions of DNA sequence that encode proteins essential for the virus to replicate. Hence, our virus infects cells but cannot replicate in them to produce more of itself. The infection permits our gene to be expressed in cells in the inner ear so we can learn if our gene replacement restores hearing function. The infected cells cannot make more viral particles, and they therefore do not harbor infectious AAV viral particles.

The animals we seek to ship to our colleague in Germany were infected with the replication defective AAV virus when they were embryos growing in the uterus of the female mouse. They are born about a week later, mature to 21 days, and are then tested for hearing function. The next step is to have the sensory hair cells evaluated by electrophysiology; our colleague in Germany is one of the only people on earth who does the specialized kind of recordings necessary to validate hair cell function. There are no other options for us to secure the electrophysiological analyses.

We are highly confident that the adult mice that were exposed to AAV when they were embryos growing in the uterus do not shed virus: they cannot since they are unable to make new virus. The AAV virus we use is simply a gene shuttle to bring our cargo, the genes of interest, into the target cells in the inner ear, very similar to the AAV viral vectors used for human gene therapy. We believe our mice pose no risk whatsoever to other mice, rodents, or humans.

We have generated 30 adult mice to date that were exposed to experimental and control virus. We had 4 possible ship dates for these animals that have all passed. Estimating the cost of this extremely difficult. Each injected mouse is worth about $200 USD given what it costs to generate the animals, maintain them, and perform the surgery and injections. This is therefore about $6,000 lost thus far, and it's probably a low estimate. I have not figured in the technician salary time to perform the preoperative and postoperative care, or my salary as I do all of the injections. But more important than the money lost is the complete breakdown of basic science research that has occurred: we cannot advance this project further without the electrophysiological recordings.

I hope that providing you with these details will help the DOT and FAA critically evaluate our request for a passenger flight permit to get these mice to Germany. I am happy to fly to the DOT or the FAA home offices at my expense and present a session on replication defective AAV virus if requested.

I do appreciate your support of our efforts.

John

From: Debra Brickey
Sent: Thursday, July 30, 2009 12:53 PM
To: John Brigande; Sally Finch
Subject: Animal shipment to Germany

Hey John,

I spoke to Kenneth Herzog and he had heard from the FAA and their suggestions and then said it had to go to a technology advisor. I tried to explain more fully to Kenneth that the mice should not be categorized as Category B because there was no longer live virus in the animals.

He asked me to write up an explanation to give to their technology representative but I first wanted to confirm my understanding of what happens with you John and also give an estimate of cost including time spent on the missed two previous shipments due to delays in getting this approval.

So, my understanding is that the adenovirus construct is injected into embryos in the inner ear cells. The adenovirus expresses the prescribed proteins but since it cannot replicate it would be gradually degraded and expression lost as the animal develops (it does not integrate into the DNA correct?). By the age of shipment the animals would no longer have adenovirus in their bodies. So that the animals are essentially pathogen free.

Do you want to add anything to that or clarify any part of that? Please let me know your costs and comments ASAP since I would like to email this to him later today or early tomorrow?

I apologize for all the hassle this has caused for you.

Debra