# Practical Considerations for the Use of *In Vivo* AAV-Based Gene Therapies: Q&A

The "Practical Considerations for the Use of *In Vivo* AAV-Based Gene Therapies" webinar was held on November 6, 2019. This webinar was presented by Chris Jenkins, PhD, MPH, RBP, CHMM, Principal Partner and Chief Gene Therapy Biosafety Officer at Clinical Biosafety Services.

This document includes participant questions that were raised during the live webinar, as well as additional participant questions, with answers provided by Dr. Chris Jenkins. The information and responses captured below represent expert advice and guidance from Dr. Jenkins, a member of the GTnetwork Steering Committee. The advice and guidance provided do not necessarily reflect the opinions of AveXis, Inc nor other members of the GTnetwork Steering Committee.

## Questions Answered During the Live Webinar

1. **Where do most centers administer these infusions? Inpatient? Clinics? Negative pressure rooms?**
    - Location would depend on several factors such as:
        - Type of agent (e.g. adeno-associated virus [AAV], herpes simplex virus) and its associated risk
        - Manufacturer's guidance
        - Type of facilities
        - Type of drug
    - For the majority of U.S. Food and Drug Administration-approved intravenously delivered products, infusions can be carried out in infusion centers with dedicated rooms

2. **What facility designs and equipment should hospital pharmacies start incorporating to handle new gene therapies in the pipeline?**
    - Until National Institute for Occupational Safety and Health (NIOSH) updates are available, the recommendation would be that each institution develops its own procedures and evaluates gene therapy products individually
    - The risk group and biosafety level of each viral vector should be taken into consideration
    - Centers may require the use of biosafety cabinets, which protect the individual, the environment, and the biological product

- Many pharmacies have moved toward utilizing the Class II, Type B2 cabinets with 100% air filtered through high-efficiency particulate air (HEPA) filters, which allows for both biological and chemical reagents, such as chemotherapies
- Pharmacies have been getting ready to update their intravenous rooms from USP 797 to USP 800 (standards provided by the U.S. Pharmacopeia [USP] Convention)
- Clean benches should not be used – they blow clean air at the product but do not protect an individual at the bench

3. **Any practical information for preparation in a hospital pharmacy cleanroom?**
    - USP 797 and USP 800 standards are what pharmacies will have to follow
        - USP 797 provides information on standards for preparing compounded sterile medications
        - USP 800 provide standards for safe handling of hazardous drugs to minimize the risk of exposure to healthcare personnel, patients, and the environment
    - Those standards have not yet become official
    - NIOSH publishes a list of hazardous drugs. Currently, gene therapies are not included in the NIOSH list of hazardous drugs, and the next update is expected in 2020

4. **Is a closed system transfer device (CSTD) recommended for preparation?**
    - This is an institutional level decision, and we have seen institutions increase usage of CSTDs when handling AAV vectors
    - CSTDs reduce exposure to individuals preparing a product by mechanically prohibiting the transfer of environmental contaminants into the system and the escape of the hazardous drug or vapor concentrations outside the system

5. **For the pharmacy preparing the dose(s), what is required for deactivation/decontamination of the AAV vectors?**
    - Some viruses are a little more hardy than others, so you have to use more than soap and water on them
    - The Environmental Protection Agency (EPA) publishes a list of disinfectants. An EPA-listed disinfectant that is appropriate for the agent should be used (e.g. 10% bleach with the appropriate contact time), as per the disinfectant product label. Most clinics, hospitals, and academic centers use anything from 10% bleach to 70% ethanol

- Refer to the National Institutes of Health Pathogen Safety Datasheets (PSDS) or product material provided by the manufacturer – these provide information regarding virus susceptibility
- Bleach is effective but causes pitting of stainless steel units. Therefore, many institutions prefer to use PDI Sani-Cloth® wipes, which may be bleach-based or quaternary ammonium-based, followed by sterile water to prevent pitting.

6. **What are the recommendations or options for waste stream?**
    - Waste stream depends on the city, state, and county of each institution
    - Biologics typically get autoclaved or heat pressurized, and treated as a biohazard with red containers
    - Chemotherapeutic agents get incinerated, which is a higher level of inactivation
    - Therefore, biologics and chemotherapeutic compounds are sometimes just merged together in a yellow chemotherapy waste container for ease and space considerations – this way, both the biologics and chemotherapeutic waste are compliant, but treated at a higher level

7. **How much do you anticipate that immune reactivity in caregivers and siblings will limit any future children in that family from receiving AAV-based gene therapy?**
    - The risk of seroconversion from contact with patients receiving any gene therapy product is not known
    - Generally speaking, the manufacturer's guidance should be consulted to develop product-specific procedures with regard to vector shedding in order to minimize inadvertent exposure to the vector
    - Population studies have shown that the risk of seroconversion with AAV increases over a person's lifetime, and that there is an increase in anti-AAV antibodies
    - Anti-AAV antibody levels are generally low in children and care should be taken to minimize potential exposure to AAV vectors, particularly in young family members of a patient receiving gene therapy

**<u>Additional Participant Questions</u>**

8. **Is AAV inactivated by quaternary ammonium compound disinfectants?**
    - AAVs are typically inactivated by quaternary ammonium compound disinfectants but this can vary across treatments
    - It is recommended that the approved prescribing information is consulted for more information

9. **What are your thoughts about inactivating leftover drug in the vials prior to disposal?**
    - Although the biological risks from handling AAV vectors are considered very low, it is normal and acceptable that any leftover AAV vectors are inactivated before disposal
    - It is important that no manipulations are made in pulling the leftover drug from the vial

10. **What are some safety considerations for nurses involved in treating patients with gene therapy infusions?**
    - Personal protective equipment should be worn by nurses while manipulating the drug in case the infusion bag is separated or dropped during the infusion. These should include:
        - Lab coat/disposable gown
        - Gloves
        - Eye protection
        - Mucus membrane protection
    - The eye protection and mucus membrane protection can come off once the infusion is underway, and also so as not to alarm the patients and families

11. **Would you recommend that healthcare professionals (HCPs) who come in contact with AAV-based gene therapy monitor their own anti-AAV antibody titers over time (i.e. get a baseline value then monitor)? If yes, how frequently should one measure anti-AAV antibody titers?**
    - No, I would not recommend that HCPs who come into contact with AAV-based gene therapy should monitor their own anti-AAV antibody titers over time
        - Evidence from clinical research suggests that AAVs are prevalent in the community and can be acquired from the environment as well as clinical settings
        - Prevalence of anti-AAV antibodies increases the older one gets (eventually rising to as high as 60% in some populations aged ≥50 years)

12. **If a patient utilizes pillows and blankets during administration of AAV-based gene therapy, how should those items be handled as far as disposal for destruction vs decontamination?**
    - Pillows and blankets used during administration of AAV-based gene therapy should be disinfected if obviously contaminated
    - The routes of exposure through shedding are significantly higher in stool, which, for some gene therapies in infants, is the most likely route of contamination