Safety Data Sheet

Creation Date: 11NOV2017 Revision Date: 08Mar2018 (REV-2.1)

1. Identification

Product Name: Adeno-associated Viral Vectors

Trade name: Not available

Other names: Adeno-associated virus; AAV Vector

Intended Use: For development of therapeutic agents; used as a delivery vehicle for gene therapy

Company: Spark Therapeutics, Inc.
3737 Market Street, Suite 1300
Philadelphia, PA 19104

Emergency Telephone Number: 1-855-772-7589

2. Hazard Identification

Adeno-associated viral vectors are used with a therapeutic transgene in gene therapies. The human health risks associated with the potential environmental exposure to AAV vectors under the conditions of normal laboratory use are considered to be very low. No environmental effects were identified during the development of the product and considering the nature of the product, and the scale and environment of use and potential release, the potential for environmental risks are also considered to be very low or negligible.

Classification:
Adeno-associated virus (AAV) is in the family Parvoviridae and the Genus Dependovirus. AAV is a non-enveloped, single strand DNA-containing virus that can only replicate in the presence of a helper virus. Known helper viruses are adenovirus, Herpes virus, and Vaccinia virus. Wild-type AAV may integrate into the host-cell genome and remain latent until an infection that provides helper virus supplies the necessary genes for replication.

AAV vectors consist of recombinant transgene sequences (such as human gene or other sequence of interest) flanked by the AAV inverted terminal repeats. AAV vector cloning capacity is limited to the size of wild-type AAV genome. Recombinant AAV vectors can infect a wide range of mammalian cell types. AAV vectors are normally provided as a suspension of purified viral particles in phosphate buffered saline.

Signal Word: Danger

Statement of Hazard:

Wild Type AAV is a non-pathogenic virus and is not known to cause any diseases in humans or animals. There is evidence of AAV infection in the human embryo and there is an association of AAV with male infertility. A significant correlation was found between the presence of AAV DNA in amnionic fluids and premature amniorrhexis (rupture of the amnion) and premature labor.

Recombinant AAV vector forms a stable extra chromosomal expression cassette in transduced cells. At very low frequency, AAV vectors may integrate into host cell DNA.

Recombinant AAV vectors produced at Spark are manufactured using a helper-virus free production system. No live helper virus is present in the AAV product.

To date, the recombinant AAV vectors produced at Spark do not contain transgene DNA that encodes for a potential mutagenic or toxic gene product. Therefore, recombinant AAV vectors produced at Spark in general can be handled in a BSL-1 environment.

When recombinant AAV products encode for a potential hazardous gene product, a product specific SDS with a different BSL classification will be issued.

Biosafety Level -1 (BSL-1) procedures for biohazards are considered appropriate.

Standard biosafety practices typically followed by medical facilities include:

- Restricted access
- Safe storage
- Training of personnel
- Availability of Personal Protective Equipment (PPE; laboratory coats, gowns, gloves and safety glasses)
- Established routine practices for dealing with potentially biohazardous materials such as patient samples/fluids and medical waste (autoclaves, sharps bins, incinerators, disinfectants and appropriate cleanable surfaces).

3. Composition/Information on Ingredients

AAV is one of several species in the *Dependovirus* genus of parvoviruses that requires helper functions supplied by co-infecting helper viruses to enable productive infection.

The natural host of AAV is humans. It does not infect plants or other microbes and is not known to be involved in environmental processes. It does not respire and does not contribute to primary production or decomposition processes. In its virion form, it does not display any metabolic activity. There are no known natural predators, preys, parasites, competitors, or symbionts associated with AAV, although it does require helper functions of co-infecting viruses for replication in nature as described above. Human AAV was discovered in 1965 as a contaminant of adenovirus (Ad) preparations. It is a globally endemic infection of humans and is thought to be spread in nature via inhalation of aerosolized droplets, mucous membrane contact, or ingestion.

4. First Aid Measures

Eye Contact: In the event of accidental eye contact, flush in an eyewash for at least 15 minutes.

Skin contact: In the event of exposure to skin, broken skin, or needle stick injury, clean the affected area thoroughly with soap and water and/or a disinfectant. For exposure to broken skin or needle stick injury, there is a possibility of adenovirus infection; treatment for adenovirus infection typically involves treating the symptoms, which are typically flu-like.

Ingestion: In the event of an accidental occupational exposure (e.g., through a splash to the mucous membranes), flush with clean water for at least 5 minutes.

Inhalation: No information

Symptoms and Side Effects of Exposure: AAV is not known to be a pathogenic virus in humans. However, if adenovirus is associated, a wide range of symptoms is possible, including flu-like symptoms, and diarrhea. The human health risks associated with the potential environmental exposure to AAV vector under the conditions of normal use are considered to be very low.

5. Fire-Fighting Measures

AAV is usually stored frozen at less than -60 degrees C (-76 degrees F) as a phosphate buffered saline solution and used in small quantities in laboratories or specialty manufacturing locations. As a result, the fire risk is expected to be very low or negligible.

Suitable Extinguishing Media: No information available

Unsuitable Extinguishing Media: No information available

Hazardous Combustion Products: No information available; none expected

Explosion Limits:	No information available; not considered an explosion hazard

6. Accidental Release Measures

Adeno-associated viral vectors are expected to be present in laboratory quantities and stored as frozen particle suspensions (viral particles in phosphate buffered saline). The potential for accidental release of substantial quantities is limited.

Health and Safety Protection: As relatively low quantities (laboratory quantities) of adeno-associated viral vectors are likely to be stored in any area, the potential for accidental release and exposure of significant biotypes, protected areas, and drinking water supplies is considered negligible.

If spills occur outside a biological safety cabinet, all personnel should leave the area of the spill and immediately wash hands and face with soap and water. The area of the spill should be secured so that people cannot reenter the area. After 30 minutes has passed, considered sufficient time for any aerosols to have settled, the room should be entered wearing appropriate PPE. The spill should be covered with paper towels and chlorine bleach (10%) applied, starting at the perimeter and working to the center. The bleach should be left in place for 20 minutes before cleanup. Once cleanup has occurred, the area should be disinfected a second time with bleach.

If spills occur inside a biological safety cabinet, the spill should be covered with paper towels or wipes and disinfectant poured over the spill area. The disinfectant should be allowed to remain in place for 20 minutes before the spill is cleaned up. Following the initial cleanup, the surface should be disinfected a second time with bleach.

Disinfectants should be used with a minimum 20 minutes contact time. Alcohol is not an effective disinfectant. Effective disinfectants include:

- Sodium hypochlorite (1-10% solution of fresh bleach; lower concentration should only be used on surfaces with higher concentration used if other organics (e.g., paper towels) are present
- Alkaline solutions at pH>9
- 5% Phenol

Environmental Protection: The risk of unintended exposure to flora and fauna is not anticipated.

Methods for Cleanup and Containment: Spills should be treated with a viricidal agent, such as 10% sodium hypochlorite, and blotting with absorbent materials, with the disinfectant and blotting material left in place for 20 minutes. Following cleanup, a second disinfection should occur. AAV contaminated materials should be disposed of as biohazardous waste. Viral stock should be disposed of by autoclaving at 121 degrees C (250 degrees F) for 30-40 minutes.

Sodium hypochlorite (10% solution), 0.5% peracetic acid, and iodine (1%) (5 or 30-minute contact time) each were able to inactivate concentrated AAV in solution, whereas 70%

isopropanol was shown not to be an effective disinfectant. Steris 0.525% Hypochlorite WFI can also be used to inactivate parvoviruses in solution and on surfaces.

7. Handling and Storage

Handling: Standard Biosafety Level 1 practices should be followed when handling adeno-associated viral vectors and any associated waste. The material should be handled as a biohazardous material.

- A biological safety cabinet (BSC; a.k.a. tissue culture hood) should be used for manipulations that can generate aerosols, such as pipetting, harvesting, infecting cells, filling tubes/containers, and opening sealed centrifuge canisters. If a procedure cannot be done in a BSC but only on an open bench, a plastic shield should be used to prevent exposure through inhalation or splashing.

- Aerosol containment devices should be used when centrifuging. These include sealed canisters that fit in the centrifuge bucket, covers for the centrifuge bucket, heat sealed tubes, or sealed centrifuge rotors. Rotors should be removed and opened inside a BSC. Centrifuge tubes should be filled and opened in a BSC.

- Vacuum lines should be protected with liquid disinfectant traps and micron filters.

- Biohazard signs and labels must be displayed in areas and on equipment where AAV is used and stored.

Storage: AAV vector is usually stored frozen at less than -60 degrees C (-76 degrees F) as a suspension of viral particles in a phosphate buffered saline. The material should be stored in a secure environment following standard biosafety practices, including restricted access and secure storage.

8. Exposure Controls/Personal Protection

AAV vector is stored as a liquid or frozen particle suspension. Universal biohazard precautions for preparation, administration and handling of AAV should be followed to avoid accidental exposure.

- Wear personal protective equipment (PPE; e.g., laboratory coat, safety glasses, and disposable gloves) while preparing or using.
- Avoid accidental exposure to AAV, including contact with skin, eyes, and mucous membranes. Cover any exposed wounds before handling.
- Treat all spills with a viricidal agent such as 1% sodium hypochlorite and blot using absorbent materials.
- Dispose of all materials that may have come in contact with AAV in accordance with universal biohazard precautions.

Analytical Method: No information available

Engineering Controls: The product should be stored in a secure environment, following standard biosafety practices, including restricted access and secure storage. A biological safety cabinet (BSC; a.k.a. tissue culture hood) is recommended for manipulations that can generate aerosols.

Personal Protective Equipment (PPE):

Eyes: Wear safety glasses while using

Skin: Wear personal protective equipment (e.g., laboratory coat and gloves) while handling AAV Vector.
Respiratory: No information provided but given the nonpathogenic nature of the AAV and the small amount administered, the potential for respiratory exposure is likely to be low.

9. Physical and Chemical Properties

Physical State:	AAV is provided in liquid or frozen particle suspensions
Odor:	No information available
Molecular weight:	No information available
Molecular formula:	No information available
Upper/lower flammability or explosive limits:	No information available
Vapor pressure:	No information available
Odor threshold:	No information available
Vapor density:	No information available
pH:	No information available
Relative density:	No information available
Melting point/freezing point:	No information available
Solubility(ies):	No information available
Initial boiling point and boiling range:	No information available
Flash point:	No information available
Evaporation rate:	No information available
Flammability (solid, gas):	No information available
Upper/lower flammability or explosive limits:	No information available
Vapor pressure:	No information available
Vapor density:	No information available
Relative density:	No information available
Partition coefficient: n-octanol/water:	No information available
Auto-ignition temperature:	No information available
Decomposition temperature:	No information available
Viscosity:	No information available

10. Stability and Reactivity

Outside of the host, AAV is relatively stable and resistant to dehydration. AAV particles are resistant to a wide pH range (pH 3 to 9) and can resist heating at 56°C (130 degrees F) for 1 hour. Recombinant AAV vectors dried on stainless steel could be detected by *in vitro* transduction for up to 6 days, although the levels decreased significantly as early as day 1. However, AAV on a stainless-steel surface was completely deactivated after steam sterilization in an autoclave (121 ºC, 30 minutes). Sodium hypochlorite (10% solution), 0.5% peracetic acid, and iodine (1%) (5 or 30-minute contact time) each were able to inactivate concentrated AAV in solution, whereas 70% isopropanol was shown not to be an effective disinfectant. Steris 0.525% Hypochlorite WFI can also be used to inactivate parvoviruses in solution and on surfaces.

11. Toxicological Information

Although considered unlikely, the possibility exists that wild type AAV can be transmitted to other humans in the environment via direct contact. However, AAV is considered to be non-pathogenic in its natural host, i.e. humans.

Despite the lack of evidence for pathogenicity of wild type AAV, correlations have been made between the occurrence of male infertility and the presence of AAV viral DNA sequences in human semen, and the occurrence of miscarriage and the presence of infectious AAV in embryonic material, as well as in the cervical epithelium. A clear association of wild type AAV with occurrence of male infertility or miscarriage has not been established from these studies. However, concern was raised because wild-type AAV has been shown to interfere with mouse embryonic development.

12. Ecological Information

Cross-species transmission of AAV species does not appear likely to occur in nature but the possibility exists that wild type AAV can be transmitted to non-human animals in the environment, either from direct contact or via fomites contaminated with bodily fluids. However, AAV is considered to be non-pathogenic in its natural host, i.e. humans, and thus not associated with any environmental effects.

13. Disposal Considerations

Following use of adeno-associated viral vector, used disposable instruments or other materials used during the preparation procedures, should be disposed of in a manner consistent with the standard practice of the institution for potentially biohazardous materials.

Spills should be treated with a viricidal agent, such as 10% sodium hypochlorite, and blotting with absorbent materials, with a contact time of 20 minutes or more. Following cleanup, a second round of disinfection is recommended. Sodium hypochlorite (10% solution), 0.5% peracetic acid, and iodine (1%) (5 or 30-minute contact time) each were able to inactivate concentrated AAV in solution. Steris 0.525% Hypochlorite WFI can also be used to inactivate parvoviruses in solution and on surfaces.

14. Transport Information

The International Air Transport Association (IATA) defines an Infectious Substance as 'A substance known to contain or can reasonably be expected to contain pathogens' and a Pathogen as 'Microorganisms (including bacteria, viruses, rickettsia, parasites, fungi) and other agents such as prions, that can cause disease in humans or animals'. Therefore, AAV is not considered an infectious substance as defined by IATA. Instructions for use, handling, and disposal accompany all shipments as part of the package insert.

15. Regulatory Information

Section (B) (5) (III) of the HCS (CFR 1910.1200) exempts drug or medical or veterinary device or product from the labeling requirements of the HCS when subjected to the labeling requirements of the Food and Drug Administration.

AAV is a non-pathogenic virus and should be handled accordingly. Given the non-replicative nature of the modified organism, the nature of the transgene, and the fact that the parent organism is not known to be pathogenic, Biosafety-1 (BSL-1) procedures are considered appropriate.

Recombinant AAV vectors produced at Spark are manufactured using a helper-virus free production system. No live helper virus is present in the AAV product.

To date, the recombinant AAV vectors produced at Spark do not contain transgene DNA that encodes for a potential mutagenic or toxic gene product. Therefore, recombinant AAV vectors produced at Spark in general can be handled in a BSL-1 environment.

When recombinant AAV products encode for a potential hazardous gene product, a product specific SDS with a different BSL classification will be issued.

16. Other Information

The information in this Safety Data Sheet (SDS) was obtained from sources which we believe are reliable; however, the information is provided without any representation or

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