This Report is cleared for submission to the Board by Marie O'Connor, Programme Manager.

Signed:  12/03/2020

Office of Environmental Sustainability

INSPECTOR'S REPORT

TO:	BOARD OF DIRECTORS
FROM:	Bernie Murray - Environmental Licensing Programme
DATE:	12 March 2020
RE:	Notification from Wellcome-HRB Clinical Research Facility, St James's Hospital, James's Street, Dublin 8 and Children's Hospital Ireland, Temple Street, Rotunda, Dublin 1 under Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) to administer a gene therapy treatment under a managed access programme (GMO Register No: G0726-01).

Notifier:	Wellcome-HRB Clinical Research Facility St James's Hospital James's Street Dublin 8 And Children's Hospital Ireland Temple Street Rotunda Dublin 1
GMO Register Entry No:	G0726-01
SNIF No[1]:	B/IE/20/01
Notification under Article 14(1) of S.I. No 500 of 2003:	The deliberate release of a genetically modified organism for purposes other than placing on the market.
Timeframe for EPA's Decision under Article 18(5) of S.I. No 500 of 2003:	A person shall not deliberately release a genetically modified organism (GMO) for purposes other than placing on the market unless consent in writing has been granted by the EPA. The EPA shall communicate its decision (either grant consent with or without conditions

[1] Summary Notification Information Format (SNIF). Summary of the notification forwarded to the European Commission for circulation to all member states.

	or refuse consent) in writing to the notifier within 90 days of receipt of the notification.
Date of receipt of notification under Article 14 of S.I. No 500 of 2003:	25 February 2020
Request for additional information under Article 19 of S.I. 500 of 2003:	09 March 2020
Additional Information submitted under Article 19 of S.I. 500 of 2003:	10 March 2020
Date by which decision is required:	18 March 2020
Representations to the EPA relating to this notification under Article 16 of S.I. 500 of 2003:	0

Introduction

Wellcome-HRB Clinical Research Facility (CRF), St James's Hospital, James's Street, Dublin 8 and Children's Hospital Ireland, Temple Street, Rotunda, Dublin 1 sought the consent of the Environmental Protection Agency (EPA) on 25 February 2020 to administer AVXS-101 gene therapy treatment to paediatric patients under 2 years of age, diagnosed with spinal muscular atrophy (SMA), caused by mutations in the survival motor neuron 1 (SMN1) gene.

Mutations in the SMN genes result in decreased expression of the SMN protein which correlates directly with death of the individual's motor neurons. Loss of motor neurons leads to progressive loss of muscle control, strength and function, swallowing, breathing and, ultimately, death. SMA Type 1 is characterised by decreased muscle tone and severe weakness from early infancy. These children never attain the ability to sit without support and have a median survival (defined by the endpoint of death or the requirement for permanent ventilation) of 10.5 months.

SMA is a rare autosomal, recessive condition occurring in 1/11,000 heads of population. According to the notifier, there were 20,686 individuals affected by SMA in the EU in 2017 (latest figures).

There are limited treatment options for patients with SMA. The EU Commission granted a marketing authorisation in May 2017 for Spinraza (nusinersen), designed to increase the production of the SMN protein. Clinical studies with nusinersen have shown some promise in improving motor function. However, it must be administered indefinitely every 4 months via intrathecal (into the spinal canal) injection and requires a lengthy induction period prior to effectiveness, and has safety considerations which require clinical monitoring.

The goal of AVXS-101 treatment is transduction[2] of motor neurons by a viral vector containing the gene for SMN, which results in increased SMN protein expression in motor neurons, thereby preventing cell death, improving neuronal and muscular function, and increasing overall patient survival. The SMN gene present in AVXS-101 is not integrated into the patient chromosome but resides as episomal DNA in the nucleus of transduced cells and appears to be highly stable in motor neurons or muscle cells.

AVXS-101 is a recombinant adeno-associated virus based vector which has been designed to express the survival motor neuron 1 (SMN1) gene in paediatric patients less than 2 years of age with SMA.

It is proposed that this deliberate release will be carried out in the Clinical Research Facility, St James's Hospital, James's Street, Dublin 8.

The notification was submitted by the notifier in accordance with Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) (for purposes other than placing on the market) .

Considerations for the Board

Role of the EPA in reviewing this notification

The Agency's responsibility under the Genetically Modified Organisms (Deliberate Release) Regulations (Article 18, S.I. 500 of 2003) is to evaluate the risks posed by the proposed deliberate release for human health and the environment and to give consent to the release only if satisfied that it will not result in adverse effects to human health or the environment.

The responsibility of the Agency relates to the wider environment and the general population. In its review of the application, ELP have considered:

- the patient receiving the treatment insofar as they are part of the general population and the wider environment;
- the potential risk of the GMO moving from the patient to the general population and the consequences of such a risk; and,
- potential risks for the environment at large.

Description of the Genetically Modified Micro-Organism for use in the proposed deliberate release

AVXS-101 is a recombinant, non-replicating, non-integrating, adeno-associated virus serotype 9 (AAV9) capsid shell containing the cDNA of the human Survival Motor Neuron (SMN) gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB) as well as two AAV inverted terminal repeats (ITR) from the AAV serotype 2 (AAV2).

Purpose of the proposed deliberate release

To administer AVXS-101 gene therapy treatment to paediatric patients under 2 years of age diagnosed with spinal muscular atrophy (SMA). Patients will be treated

[2] the process by which foreign DNA is introduced into a cell by a virus or viral vector

and followed-up as part of the AveXis[3] global managed access programme to provide the gene therapy product to eligible children in advance of European licensing.

Proposed location of the deliberate release

The proposed deliberate release (administration of the GMO) will take place in the Wellcome-HRB Clinical Research Facility, St James's Hospital, James's Street, Dublin 8. Patients will be followed up at Children's Hospital Ireland, Temple Street Hospital, Temple Street, Dublin 1.

A gene therapy trial is currently underway in the CRF to test a gene therapy product for haemophilia (G0667-01). The CRF was also the location of a previous clinical trial (G0536-01) from July 2014 to December 2016 to assess Hepatitis C vaccines.

Timeframe for the proposed deliberate release

This proposed release will take place from the date of issue of the consent to 31st December 2020.
One patient will be treated imminently with the possibility to treat a further three patients.

The Notifier

The notifier in this instance is Wellcome-HRB Clinical Research Facility, St James's Hospital, James's Street, Dublin 8 and Children's Hospital Ireland, Temple Street, Rotunda, Dublin 1.

The notifier has requested that this application be expedited owing to the need for the immediate treatment of an eligible patient.

Dr Declan O'Rourke, Department of Neurology, Temple Street Hospital is the primary treating Physician for the child and retains all clinical responsibility for the care plan and management of the child during the 60 day shedding period post-infusion.

Professor Hennessy is responsible (through the CRF) for providing professional services to Dr O'Rourke, his team and the patient with respect to all aspects of the activities taking place at the CRF site. In addition to correct dosing and administration of the gene therapy product, these include receipt, storage, release, and disposal of the GMO.

Professor Hennessy is the Principal Investigator responsible for the deliberate release activity.

In accordance with Article 18(5) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003, the Agency is required to respond to the notifier in writing indicating that consent is either granted with or without conditions or refused, with reasons for the refusal.

[3] AveXis Inc own the gene therapy product AVXS-101. Novartis are the parent company.

The notifier submitted a risk assessment in accordance with Article 5(2) and the Second Schedule of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003.

AAV infections are common in humans but they are not associated with disease. In excess of 90% of the human population is seropositive for AAV. AAV is designated a risk group 1 biological agent ('one that is unlikely to cause human disease') in accordance with Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. Wild type AAV (wtAAV) needs a helper virus such as adenovirus or herpes virus to replicate. The wtAAV genome carries two genes for capsid formation (cap) and DNA replication and packaging (rep). AVXS-101 does not contain the *rep* and c*ap* genes. Thus, AVXS-101 is replication-defective, even in the presence of a helper virus.

Recombinant AAV based vectors are usually classified as Class 1 activities (no or negligible risk).

The recombinant AAV9/AAV2 based vector used for the production of AVXS-101 has been engineered to contain the insert which is the human SMN cDNA expression cassette flanked by AAV2 Inverted Terminal Repeat sequences which are required for viral DNA replication and packaging of the rAAV vector genome and a cytomegalovirus promoter to drive gene expression.

AVXS-101 will be administered intravenously following which it will specifically target motor neurons. In the cell, multiple AVXS-101 genomes assemble to form larger double stranded DNA concatemers[4]. These concatemers persist in the cell as stable extrachromosomal structures and are transcriptionally active.

None of the sequences of the inserted transgene are known to have pathogenic or harmful characteristics. As the vector construct is replication defective (owing to deletion of *rep* and *cap* genes), even in the presence of a helper virus, no new progeny viruses are being produced. Thus, the pathogenicity of AVXS-101 is considered by the notifier to be even less than that of AAV2 or AAV9 viruses, which are already considered non-pathogenic.

Risks to the patient receiving the treatment insofar as they are part of the general population and the wider environment;

Immune response

Administration of the GMO to the patient will elicit an immune response to AAV capsid and the expression of the SMN protein.

Recombination of the viral vector

Recombination is where there is an exchange of genetic material between the viral vector and other viruses.

Since AVXS-101 contains the ITR-sequences of AAV2, there is a possibility of recombination of the vector with wild type AAV2. It would require simultaneous

[4] A concatemer is a long continuous DNA molecule that contains multiple copies of the same DNA sequence linked in series.

infection of one-and-the-same cell with AVXS-101, wtAAV2 and a helper virus. The result of such a recombination would be that AVXS-101 would gain functional genes of the AAV2 required for replication and encapsidation, but, in turn, would lose the transgene. AAV has limited packaging capacity making it unlikely that the AAV vector will contain both the *rep* and *cap* genes and the transgene cassette. Replication competent AVXS-101 particles would not be formed. Recombinant replication deficient particles could theoretically be formed but they would carry the same characteristics as AVXS-101 and wtAAV2.

Insertional mutagenesis

There is a theoretical risk that AAV infection could lead to insertional mutagenesis caused by non-site-specific integration of the AAV genome into the host-cell genome of infected cells. However, to date there has been no documented insertional mutagenesis in clinical trials involving recombinant AAV. Consequently, the risk for germline transmission is negligible.

The potential risk of the GMO moving from the patient to the general population and the consequences of such a risk;

Shedding

Following administration of AVXS-101, shedding of vector DNA in urine, saliva and faeces is expected to continue for a few weeks.

A shedding study carried out in humans by AveXis Inc. demonstrated that AVXS-101 is detectable in shed samples from day 1 post-infusion. Concentrations in urine and saliva were 0.1% to 0.01% of the initial concentration in the body at day 1 post-infusion falling to levels below the limit of quantitation. In stool, levels 10% to 30% of the initial concentration in the body were detectable at day 1 post-infusion. Overall, AVXS-101 was primarily cleared from the body in stool and the levels were below the limit of quantitation by day 60 post-infusion. Even in the case of shedding the AAV vectors do not propagate outside of cells.

Where non-target individuals become exposed to AVXS-101 (for example through shedding) it may similarly result in the expression of SMN protein (which is human in origin) and induce an immune response to AVXS-101 capsid protein. Bearing in mind that the non-target individual will be exposed to much smaller amounts than the original dose administered to the patient, it is expected that the ensuing effects will also be much reduced compared to patients. Since the AAV vector is replication incompetent further shedding is deemed to be negligible.

Parents of the patient and carers will be provided with clear and detailed instructions (condition 6.7) identifying the bodily fluids that are potentially contaminated with vector DNA and how these fluids should be cleaned up and the waste properly disposed of to minimise the potential for unintended exposure.

All GMM contaminated waste generated will be collected by SRCL Ltd, taken to their Kylemore Road facility from where the waste will be sent to a European based hazardous waste facility for treatment. Both the CRF and Temple Street Hospital have service agreements in place with SRCL Ltd.

The potential risks for the environment at large.

Wild type AAV is not known to be involved in environmental processes.

There is no potential for release into the environment through shedding directly from the patient as soiled nappies etc will be collected and sent for incineration

Due to the low numbers of vector DNA copies, horizontal gene transfer is highly unlikely. Even if horizontal gene transfer occurred, the sequences would not confer a selective advantage to other organisms such as bacteria since AVXS-101 does not contain any prokaryotic promoters, any antibiotic- or other types of resistance genes or any genes, which would enhance or constrain their growth. Therefore, it is unlikely that AVXS-101 would have an effect on the natural dynamics of microbial populations or the biogeochemical cycles at any given site in the environment.

According to the notifier, AAV is relatively stable in the environment. AAV is sensitive to appropriate virucidal disinfectants.

Storage, preparation and administration of the vector

AVXS-101 will be shipped frozen on dry ice to the CRF on a patient-by-patient basis. It will be stored in a designated fridge at 2–8°C within the Pharmacy which is swipe card access restricted to authorised personnel. The gene therapy product must be used within 14 days. The CRF Pharmacist will be responsible for the receipt, storage and preparation of the drug prior to administration.

AVXS-101 will be removed from 2-8^{o}C storage only when ready to use. The dose volume is dependent on the patient weight. A dosing syringe will be filled (needle-less system) in the pharmaceutical isolator and fitted to an infusion set before transfer in a biohazard transport box to the isolation room where patient administration will take place. Aseptic techniques will be applied throughout.

The GMO must be administered within 8 hours of preparation. Administration is by intravenous infusion over a period of one hour. Any remaining product in the infusion set must be flushed through with saline to ensure the patient receives the intended dose.

Worker protection measures taken during the release

Preparation of the gene therapy product will be performed under aseptic conditions in a dedicated pharmaceutical isolator (condition 6.5) which maintains a Grade A Good Manufacturing Practice (GMP) environment. This is a closed system under negative air pressure and the extract air is HEPA filtered. It ensures that the gene therapy product does not come into contact with the environment. Furthermore, the potential for a needlestick injury to occur is negligible since a needle-less system will be used to take up and administer the drug. The pharmaceutical isolator is contained in a clean room (under positive air pressure) which will operate at Grade D GMP and access to the clean room is restricted to pharmacy staff.

Intravenous administration of the GMO will take place in an isolation room adjacent to the clean room. Access to the isolation room is swipe card restricted. The primary treating Physician and Director of the CRF and their respective teams will wear PPE such as a mob cap, gown, face mask, double gloves, overshoes and glasses (condition 6.2). All PPE will be disposed in biohazard waste after use.

Access to the facility will be restricted to trained designated staff (condition 4.3). Prior to the commencement of the proposed release, all staff involved will undergo training in accordance with SOPs set out under condition 6.8 (condition 7.2).

Condition 6.8 requires the implementation of SOPs relating to the performance of the GMO deliberate release activity within the facility and worker protection measures.

Waste production, treatment and disposal

Spill kits will be made available during all the steps involving AVXS-101 (transport, preparation and administration) to counteract any spillage (condition 6).

GM contaminated waste generated in the pharmaceutical isolator and surrounding areas and the isolation room includes; all disposable equipment used in PPE (gowns, masks, glasses, gloves, overshoes, mob caps). It also includes all equipment used in making up the product (vials, syringes, needle-less system, saline flushes, labels, wipes, isolator gloves and tubing, luer lock caps, paper coverings, foil trays and any left-over product (less than 1 ml), paper sheets and bedlinen, other sundries).

All GM contaminated waste will be placed in 60 litre biohazard bins provided by SRCL for this purpose. It is the responsibility of the Pharmacist to ensure that SRCL is contacted promptly and that waste is collected via an a pre-agreed route into the Hospital and removed through a pre-agreed route. The waste will be stored at the Kylemore Road facility (G0163-01, W0054-02) prior to being sent for incineration to one of the following hazardous waste facilities: AGR, Germany; Redmondis TRV, Germany; or, Indaver NV, Belgium. Waste generated in the CRF is traceable through SRCL from generation to destruction and logged as having come from the CRF.

Waste generated in Temple Street Hospital includes clinical disposable waste such as, nappies and bedlinen, which will be placed in biohazard bins and removed by SRCL from Temple Street.

All sharps waste (including but not limited to: contaminated vials; syringe; infusion set and line and patient cannula) will be disposed of in sharps bins which will be locked, deposited in 60L capacity biohazard bins along with contaminated non-sharps solid waste. The biohazard bins will be handled as described above and in accordance with Condition 8.

Condition 8 requires that bins are labelled, display biohazard signs, are unbreakable and leakproof. In addition, the notifier is required to retain GMM waste inactivation records to be made available to the Agency on request.

The treated patient will be retained in the CRF for approximately 3.5 hours for purposes of observation before being transferred back to Temple Street Hospital where he/she will remain for 24 hours before being discharged.

Since this is not a clinical trial, stool samples will not be monitored for shed vector. It is accepted that shedding will occur in saliva, urine and faeces.

Condition 6.7 requires that instructions be given to parents / carers regarding the use of protective gloves if/when coming into direct contact with patient waste as well as good hand-hygiene for 60 days post-infusion.

Representations made in respect of the notification

Any person may make a representation in respect of matters relating to the deliberate release of the GMO within a 28-day period beginning on the date of publication of the notice in the newspaper, in accordance with Article 16 of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003. The notice was published in "The Irish Times" newspaper on 27th February 2020 and the last date for submission of public representations is 25th March 2020.

The notifier requested that the processing of this notification be expedited to allow for the administration of AVXS-101 to an eligible patient on the 19th March, before the end of the consultation period, on clinical grounds.

In an effort to accommodate these extraordinary circumstances, The Agency in response to this placed a further advert in "The Irish Times" newspaper on 11th March 2020 requiring the submission of representations on or before 12th March 2020.

No public representations were received up to and including 12 March 2020.

Review of the notification by the EPA and external consultation

The Agency's review of the notification involved both an external and internal review.

External Review

Review of the GMO Advisory Committee

The GMO Advisory Committee

The Agency consulted the GMO Advisory Committee (GMO AC) on this application and received 4 replies none of which expressed concern provided all procedures are followed as stated in the Environmental Risk Assessment.

One committee member indicated that he had no concerns while another stated that he did not identify "*any realistic adverse impacts from humans, animals or the environment due to the controlled use of this product for these rare patients*"

A further Committee member made the following comments:

1. *The information provided deems the risk to health of non-patients as low. However, page 13 of the ERA refers to the transmission to non-target subjects via needlestick injuries – if consideration is given to EU directive 2010/32/EU on the prevention of sharps injuries in the healthcare sector during the development of the product any risk would be further minimised. Where possible the product should be designed so that the product is delivered without the use of additional sharps or can be used with safety engineered sharps.*

   Agency Response

   The gene therapy product will be prepared in a pharmaceutical isolator and administered to the patient using needle-less systems ('Equashield' – a closed system transfer device) thereby preventing the potential for needlestick injuries.

2. *Kanamycin is used as a selection marker in the production of the product – although low risk in the end product, where possible alternative selection markers should be used so that employees preparing the initial product are not exposed to antibiotics increasing their risk of developing antibiotic resistance.*

   Agency Response

   The use of plasmid backbones devoid of antibiotic resistance marker genes would be preferable but this is a matter to be addressed at the research stage. As already outlined aseptic technique is applied throughout for the protection of both the worker and the product. All waste is treated as biohazard waste and consequently Kanamycin resistance marker genes will not be deposited or released into the environment.

3. *Shedding via faeces appears to be the main shedding route. As the product is targeted at patients under the age of 2, the virus will more than likely be shed in disposable (and hopefully not reusable) nappies. Are nappies being treated as healthcare risk waste or normal waste within the administration centre? Although deemed low risk for human health is there a potential environmental risk on return to the patient's home? Nappies will be disposed of in the domestic waste stream – will this waste stream go direct for incineration or will it go to a waste transfer station where it is possible rats etc. could interact with the waste? The SNIF states that it is not known whether zoonosis occurs in nature, nor whether other species can act as carriers or vectors under natural conditions.*

   Agency Response

   Disposable nappies will be used and all soiled nappies will be treated as biohazard waste within the CRF and in Temple Street Hospital. Once the patient returns home, it will be arranged that all soiled nappies / gloves and wipes will be collected by SRCL Ltd, taken to their Kylemore Road facility facility from where the waste will be sent for incineration to one of the following hazardous waste facilities: AGR, Germany; Redmondis TRV, Germany; or, Indaver NV, Belgium. Both the CRF and Temple Street Hospital have service agreements in place with SRCL Ltd.

4. *Due to the nature of the product, are any special conditions required for laundering of the nurses or parent's/guardian's clothes if contaminated by stool e.g. sealing in a red alginate bag prior to washing at a specified temperature?*

Agency Response

During the course of trials carried out, AVXS-101 was primarily cleared from the body in the stool and by day 60 post-infusion it was less than the limit of quantitation. Since this is not a clinical trial, stool samples will not be monitored for shed vector. Patient families will however be issued with an instruction sheet identifying the bodily fluids that are potentially contaminated with vector DNA and how to clean up these fluids and properly dispose of the waste. They will be instructed to follow these directions for a period of 60 days post-infusion. The AAV vector is not pathogenic and cannot replicate.

The medical team preparing and administering the drug will wear disposable PPE (gowns, masks, glasses, gloves, overshoes, mob caps) which will be treated as biohazard waste.
Parents will be advised to use disposable aprons. Clothes can be laundered in the normal way at home

5. *The leak-proof containers used for disposal, are these standard sharps boxes etc. or are they referring to putting open vials into another container prior to putting into the sharps box?*

Agency Response

GM contaminated sharps will be placed in puncture resistant sharps boxes which in turn will be placed in 60L biohazard bins before removal for inactivation by SRCL Ltd.

6. *Patients only stay in intensive care for 24 hours post administration/up to 48 hours prior to being released home. One patient showed a post-infusion concentration of 280% of the initial concentration after 14 days. The information provided states that shedding continues only for a short period (max. 60 days) and overall levels are below the limit of quantitation after 60 days – should the shedding in this patient's stool be monitored prior to release home and if high should the patient stay for an additional time in the centre? Page 17 refers to the patient's family taking precautions for a minimum of 4 weeks should this be extended to cover the 60 days?*

Agency Response

Shedding samples from saliva, urine and stool were collected from patients in a Phase I clinical trial in the US during which one patient showed a peak concentration in stool at day 14 post-infusion of 280% of the initial concentration in the body. The study report did not provide an explanation for this.

In contrast, three patients showed a concentration of <1% of initial concentration in the body at day 14 post-infusion, with concentrations declining approximately 4 logs (10,000-fold) over 30 days post-infusion. Overall, AVXS-101 was primarily cleared from the body in the stool and by day 60 post-infusion was below the limit of quantitation in the stool. Concentrations of vector shed in saliva and urine are quite low and are approaching the limits of quantitation within days post-infusion.

Shedding is reported to be dependent on the dose and route of administration; the IV route can be considered a worst case scenario for AAV shedding. However, even in the case of shedding, the AAV vectors do not propagate outside of cells.

The mitigation measures for clinical use provided in the risk assessment indicate good hand hygiene for a minimum of 1 month post-infusion. This includes regular hand washing and the use protective gloves and disposable aprons during nappy changes etc. As this is not a clinical trial the patient's stool will not be monitored for vector shedding. Parents / carers will be issued with instruction and it will be recommended that these instructions be adhered to for a period of 60 days post-infusion.

7. As per other ERAs, contact times and concentrations for the exact disinfectant type and the specific type and EU standard of PPE should be stated.
Agency Response

Disinfectant	Concentration	Contact time
Klericide	580ppm	10 minutes
Conc bleach	500ppm	10 minutes

The Recombinant AAV is a Class 1 GMM requiring level 1 containment.
The HSA Guidelines to the Safety, Health and Welfare at Work (Biological Agents) Regulations 2013 recommends that for biosafety level 1 (which corresponds to containment level 1), laboratory coats, gowns or uniforms be worn to prevent contamination of personal clothing. Additionally face or eye protection may be required when performing procedures that have the protential to create splashes.

The containment measures that are being applied by the notifier in this instance, in many ways exceed the requirements for a Class 1 GMM under the GMO (Contained Use) Regulations, 2001 to 2010. The emphasis is on protecting the product and patient from contamination.

All of the PPE to be worn is CE marked which means it conforms to the European Union (Personal Protective Equipment) Regulations 2018.

The masks in use (Type IIR, EN 14683) are appropriate for situations where exposure to blood and/or bodily fluids from the patient or work environment is a risk for the healthcare worker.

Nitrile gloves (EN 455) and long gloves (EN 374-2) are protective against viruses.

A fourth member of the GMO AC who is a Virologist responded as follows:
"I have no real concerns regarding the accidental exposure of unintended people to this product due to leakage etc as the GMO is replication incompetent and the only way it could spread is if a cell containing the recombinant adenovirus DNA became infected with wildtype virus which would be highly unlikely. Even if this were to happen, most of us have immunity against adenoviruses so the resulting virus would be eliminated hence limiting excretion and the spread of the recombinant virus.

As described, in my opinion I think this GMO does not pose a substantial environmental risk"

Consultation with other regulatory bodies and Government Departments

Under European and Irish legislation, medicinal products must be authorised before being marketed. In Ireland, there are two exemptions from authorisation that are relevant to patients for the treatment of conditions where there are medical needs that cannot be met by authorised medicines. These are:

- Supply through participation in an approved clinical trial; or
- In accordance with the specifications of a practitioner for use by his individual patients on his direct personal responsibility, in order to fulfil the special needs of those patients.

Patient treament with an unauthorised drug substance under a managed access programme is outside the remit of the Health Products Regulatory Authority (HPRA).

The authorised wholesaler must import the exempt medicinal product (EMP) and must notify the importation of an EMP to the HPRA. However, the HPRA does not issue an approval for importation of a particular product.

The authorised wholesaler in this instance is Uniphar who have a contract with Novartis (AveXis Inc parent company).

Consultation with other EU member states

1. Publication of SNIF
   The Agency submitted the Summary Notificaiotn Inforamtion Format (SNIF) to the European Commission in accordance with Article 18(1) of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003. The Commission published the SNIF on JRC-GMO-WebSNIF and circulated it to all other EU member states for comment on 27th February 2020 and the last date for submission of comments by other EU Member States (MS) is 28th March 2020. The Agency informed a contact in the JRC that owing to the extraordinary circumstances relating to the notification, the Agency would issue its decision ahead of the final date for receipt of EU MS comments.

   No MS comments were received up to and including 12 March 2020.

2. Notifications submitted to other EU Member States

   Clinical trial applications in respct of AVXS-101 have already been submitted in other EU MS, notably, BE, DE, ES, FR and NL. The notifications submitted in DE, ES and NL were regulated under deliberate release legislation while those submitted in BE and FR were regulated under the contained use legislation.

   There have been subsequent notifications to BE, FR and most recently DE (possibly other member states as well) for the use of AVXS-101 gene therapy products under a managed access programme, however, in all cases these notifications were preceded by the performance of clinical trials. In Belgium the Biosafety Advisory Council considered that there was no

need to perform a new environmental evaluation and that the same precautions as for the clinical trial would apply.

This notification for the use of AVXS-101 gene therapy product in a managed access programme in Ireland has not been preceded by a clinical trial therefore all procedural aspects related to Part II of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 (for purposes other than placing on the market) were followed.

Internal review

The EPA has reviewed the notification and the additional information received.

Site Inspection

A site inspection of the CRF was carried out on 6th March 2020 during which I met with the Professor Martina Hennessy, Director of the CRF, the Pharmacist, and Assistant Director of Nursing all of whom will form part of the CRF team.

I also met briefly with Dr O Rourke, the primary treating Physician for the child based in Temple Street Hospital. He along with his accompanying paediatric team will administer the gene tharapy to the patient. Between the CRF and Temple Street Hospital, six persons in total will be involved in this gene therapy treatment.

The life cycle of the GMO from its receipt at the facility, storage prior to use, preparation and patient administration and disposal of GM contaminated material were addressed during the site inspection. Further to receipt of the gene therapy product it will be stored at 2-8°C and must be used within 14 days. It will be prepared for administration in a pharmaceutical isolator and transferred to an isolation room for patient administraton. The containment measures that are being applied by the notifier in many instances exceed the requirements for a Class 1 GMM under the GMO (Contained Use) Regulations, 2001 to 2010. The deliberate release will also be carried out in accordance with Good Clinical Practice guidelines.

Conclusions

The notification provided under Article 14 of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 and the additional information provided by the notifier in response to a request for further information under article 19(1), contains all of the mandatory information.

AVXS-101 is a recombinant, replication-deficient, AAV-based vector that will be administered to paediatric patients under 2 years of age diagnosed with SMA. AAV is not pathogenic to humans and is not known to be involved in environmental processes.

Recombinant AAV lacks the viral *rep* and *cap* genes and consequently it will not replicate or produce viral particles. The risk of recombination is negligible. The containment level required to control the overall risk is containment level 1. Designated hospital staff will be trained in biosafety practices and the safe handling of GMOs.

The overall risk of AVXS-101 to people and the environment can be considered negligible.

Fee payable to the EPA

The appropriate fee of €3,000 as outlined in the Part IV of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) was paid in respect of a notification for a proposed deliberate release for purposes other than placing on the market.

Recommendation

I am satisfied on the basis of the review carried out that the risks posed to the environment and human health (general population) by the deliberate release of this GMO are negligible provided that all prescribed safety measures are followed.

On this basis I recommend that consent be granted, subject to conditions, to Wellcome-HRB Clinical Research Facility, St James's Hospital, James's Street, Dublin 8 and Children's Hospital Ireland, Temple Street, Rotunda, Dublin 1 for the deliberate release of AVXS-101, during a gene therapy treatment under Part II of the GMO (Deliberate Release) Regulations, S.I. No 500 of 2003 at Wellcome-HRB Clinical Research Facility, St James's Hospital, Dublin 8. The gene therapy treatment will be administered to paediatric patients under 2 years of age diagnosed with SMA.

Signed: 

Bernie Murray
Inspector
Office of Environmental Sustainability