This Memo has been cleared by Frank Clinton for submission to the Board
Signed: Bea Claydon Dated: 19 June 2013

Environmental Protection Agency
An Ghníomhaireacht um Chaomhnú Comhshaoil

# OFFICE OF CLIMATE,LICENSING & RESOURCE USE

## INSPECTOR'S REPORT

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| TO: | BOARD OF DIRECTORS |
| FROM: | Bernie Murray - Environmental Licensing Programme |
| DATE: | 19 June 2013 |
| RE: | Notification from Alan Boyd Consultants Ltd acting on behalf of the Center for Cellular & Molecular Therapeutics at the Children's Hospital of Philadelphia under Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) to conduct a clinical trial using a GMO (GMO Register No: G0498-01). |

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| Applicant: | Alan Boyd Consultants Ltd acting on behalf of<br>The Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia,<br>5th Floor Colket Translational Research Building,<br>3501 Civic Center Boulevard,<br>Philadelphia, PA 19104-4319<br>USA |
| GMO Register Entry No: | G0498-01 |
| SNIF No[1]: | B/IE/13/01 |
| 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 (Part B Release – Clinical Trial). |
| 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 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: | 12 February 2013 |

[1] Summary of the notification forwarded to the European Commission for circulation to all member states

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| Request for additional information under Article 19 of S.I. 500 of 2003: | 17 April 2013 | 6 June 2013 |
| Additional Information submitted under Article 19 of S.I. 500 of 2003: | 30 May 2013 | 17 June 2013 |
| Date by which decision is required: | 3 July 2013 | |
| Representations to the EPA relating to this notification under Article 16 of S.I. 500 of 2003: | 0 | |

## Introduction

Alan Boyd Consultants Ltd acting on behalf of The Center for Cellular and Molecular Therapeutics (CCMT) at the Children's Hospital of Philadelphia, 5th Floor Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104-4319 USA, sought the consent of the Environmental Protection Agency (Agency) on 12 February 2013 to conduct a clinical trial in patients suffering from severe Haemophilia B (Factor IX deficiency) using a Genetically Modified Organism (GMO).

The notifier (CCMT) proposes to conduct this trial at St James's Hospital, James's Street, Dublin. The notification was made in accordance with Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003)[2].

Alan Boyd Consultants Ltd, a UK based consultancy, will act as the notifier's legal representative in the European Economic Area to satisfy the requirement set out in Article 19 of the EU Clinical Trials Directive 2001/10/EC[3].

Haemophilia B is a predisposition to bleeding caused by a deficiency of blood coagulation factor IX (FIX). The disease is genetic and is fatal if untreated. It occurs mostly in men (affecting 1 in 30,000 males worldwide) of which the majority suffer from severe or moderately severe disease with FIX levels of ≤2%. The prevalence of Haemophilia B in Ireland is 1 per 12,500 males which is particularly high and among the reasons why the notifier wishes to perform the trial in Ireland.

Current treatment for the condition involves injections of FIX concentrate prepared from donated blood. Minimal elevations (of a few percent) in the levels of circulating clotting factor are sufficient to prevent much of the morbidity of the disease. This trial proposes an alternative treatment involving the infusion of a delivery virus carrying the FIX gene into the patient's veins. The virus will travel to the liver where it will produce corrected copies of FIX enabling the patient to produce sufficient amounts of FIX so that the patient will no longer need concentrate or will continue to need concentrate but less frequently.

[2] The Agency decided in October 2001 to regulate veterinary/clinical trials under the deliberate release legislation.

[3] Article 19 of Directive 2001/20/EC states "This Directive is without prejudice to the civil and criminal liability of the sponsor or the investigator. To this end, the sponsor or a legal representative of the sponsor must be established in the Community".

The GMO proposed to be released is a recombinant hybrid Adeno-Associated Virus (AAV) which has been engineered to express human coagulation factor IX (hFIX) for the treatment of patients with severe Haemophilia B (Factor IX deficiency). The GMO is called or abbreviated to AAV8-hFIX19.

## 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 on human health or the environment.

Description of the Genetically Modified Micro-Organisms for use in the proposed clinical trial

The Genetically Modified Organism (GMO) (called AAV8-hFIX19) is an Adeno-associated serotype 8, viral vector (AAV8) which has been engineered to express the gene for human coagulation factor IX (hFIX) for the treatment of patients with severe Haemophilia B (Factor IX deficiency). Patients will be injected with the hFIX gene therapy treatment.

Purpose of the proposed deliberate release

The GMO will be administered to clinical trial patients. The purpose of this Phase 1[4] trial is to test whether a single administration of AAV8-hFIX19 to patients:

- is safe and effective;
- can increase the amount of human coagulation factor IX (hFIX) in the blood of patients with severe Haemophilia B (Factor IX deficiency).

The information obtained in this study will guide the design of future studies in which a benefit to patients may be anticipated.

Proposed location of the deliberate releases

The proposed location for the deliberate release is the National Centre for Hereditary Coagulation Disorders, St James's Hospital, James's Street, Dublin 8.

This proposed trial will take place across four sites in the US, Australia and Ireland up to the end of 2015.

Timeframe for the proposed clinical trial

The notification requests performance of the clinical trial at the above named hospital location from the date of grant of the consent conditions to September 2015. The investigators (doctors) at the clinical trial location will treat approximately 3 – 6 patients during this time.

[4]Phase I: Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

It is envisaged that 15 patients will be treated across four sites in the US, Australia and Ireland.

## Environmental Risk Assessment

The notifier conducted 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.

**The wild type Adeno-associated Virus (AAV)**

Wild type AAV is ubiquitous and causes infections of the respiratory tract in humans in association with an existing adenoviral infection consequently the virus causes a very mild immune response. AAV of itself is not pathogenic and causes no known human disease. Nonetheless, in excess of 90% of the population has been exposed to the virus before entering adulthood. Furthermore, it has never been implicated as a causative agent for any disease. Wild type AAV is classified as a Risk Group 1 biological agent according to Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work under which it is defined as 'unlikely to cause human disease'.

Wild type AAV survives in the environment as a persistent infection in a host species or as a latent infection in the nucleus of some infected cells where it may remain inactive indefinitely. In order to undergo productive (lytic - giving rise to secretion of the virus) infection, wild type AAV is absolutely dependent upon co-infection by a second unrelated virus such as Adenovirus or Herpesvirus, which is called a helper virus. In the absence of a helper virus AAV can establish latency.

Wild type AAV is spread via inhalation of aerosolized droplets, mucous membrane contact or ingestion.

There are several naturally occurring serotypes of AAV. The capsid proteins determine the serotype and in this instance the parental virus is AAV serotype 8 (AAV8).

**The recombinant AAV**

Recombinant AAV has been derived from the parental strain (AAV8) by the removal of the *rep* and *cap* genes coding for non-structural and structural proteins respectively. The *rep* and *cap* genes have been replaced with an expression cassette[5] encoding human coagulation factor IX giving rise to AAV8-hFIX19. The transgene encoded by AAV8-hFIX19 is a protein, and is identical to normal human coagulation Factor IX. The gene product is therefore expected to be metabolised naturally.

AAV8-hFIX19 is unable to replicate independently even in the presence of a helper virus since it lacks the rep and cap genes for rescue/packaging.

**Risks to Human Health**

Neither wildtype AAV nor AAV8-hFIX19 is known to be pathogenic to humans. AAV8-hFIX19 is attenuated in that it is unable to replicate even in the presence of

[5] The genes and their regulatory elements

a helper virus since it lacks the *rep* and *cap* genes required for rescue / packaging.

AAV8-hFIX19 is designed to deliver a properly functioning version of the gene for normal human factor IX, to individuals with a defective FIX gene. The defective gene within the individual's genome will not be replaced. The delivered gene will be expressed in the liver cells[6] and will lead to circulating levels of FIX in the region of 2 – 10% of normal.

Immune response

Administration of AAV8-hFIX19 is likely to lead to the production of neutralising antibodies to AAV and might lead to the development of inhibitory antibodies to factor IX protein. In clinical trial results with similar constructs to date, antibodies to AAV have been detected in all subjects after vector infusion; however, no antibodies to FIX have been detected in any subject. An antibody directed against the vector capsid (AAV8) may affect the response to a subsequent administration of vector and subjects in this trial may be precluded from subsequent treatment with AAV vectors.

Insertional mutagenesis

AAV vectors have the potential to integrate into the genome of transduced cells at some low level. The major potential risk resulting from integration into the host cell DNA is an enhanced risk of malignant transformation leading to cancer. The risk of this occurring is suspected to be low based on the absence of such an event in large haemophilia animals participating in trials. Long term follow-up of animal models and human clinical trial participants administered with similar constructs to AAV8-hFIX19 has shown no evidence of liver tumour formation.

Shedding

There is potential for shedding to occur and it is considered likely that shedding of AAV8-hFIX19 will occur for a time period of approximately 2 weeks following its administration. This will be confirmed by sampling as part of the trial.
In a study with a construct similar to AAV8-hFIX19 in human haemophiliacs, vector DNA was detectable in the saliva, semen and stools within 72 hours of vector infusion and up to but not after day 15, in all participants. No vector was detected in the urine of any participant, at any time, after vector administration

Germline transmission

The risk of shedding via semen and the potential risk of germline transmission is reduced by the requirement that patients use an effective barrier contraceptive until such time as the vector is confirmed as no longer present in the semen, for at least two consecutive semen samples after vector administration.

The risk of shedding via saliva cannot be reduced. The risks of shedding via urine and stools could be mitigated by instructing patients to use household bleach following each use of the toilet. However, given the absence of identified risks of exposure of the environment to AAV8-hFIX19, these additional precautions are not considered necessary.

[6] The site of biosynthesis for factor IX (FIX)

Homologous Recombination

Homologous recombination between AAV8-hFIX19 and a wild type AAV could occur:

- if both AAV8-hFIX19 and wild type AAV were present in the same cell in the presence of a helper virus such as adenovirus or herpes simplex virus (triple co- infection). Such recombination could only result in the exchange of the hFIX expression cassette with the *rep* and *cap* genes of the wild type virus. It is not possible for the AAV genome to contain both *rep/cap* genes and the transgene, as this is beyond the packaging limit of the virion. Furthermore liver cells are not the natural target cells of helper viruses;

- during the manufacturing process - the presence of such contaminants is analysed on a batch-by-batch basis.

The potential direct effects in humans are limited to the transmission of AAV8-hFIX19 to an unintended human recipient. These potential adverse effects are expected to be the same as those which may be anticipated in patients receiving the treatment (immune response, potential for insertional mutagenesis and potential for germline transmission).

Such unintended human recipients would be limited to healthcare workers involved in the preparation, administration of the recombinant vector and collection of clinical samples, laboratory workers involved in sample preparation / analysis, and close contacts of treated individuals who may be exposed to the shed vector via saliva, semen, urine or faeces.

However, the recombinant vector is attenuated in that it is unable to replicate even in the presence of a helper virus since it lacks the *rep* and *cap* genes required for rescue / packaging. Furthermore, the dose transferred will be orders of magnitude lower than that received by patients.

Indirect effects of the release are limited to the consequences of the release of wild type AAV (through contamination of the medicinal product during manufacture or following recombination in the recipient's cells followed by shedding into the environment) and the possible fate of contaminating DNA sequences derived from the manufacturing process.

Antibiotic Resistance

AAV8-hFIXIX does not contain any gene that confers resistance to antibiotics. However, the antibiotic kanamycin is used indirectly in the manufacturing process, i.e. kanamycin resistance genes are encoded by plasmids that are used in the manufacture of AAV8-hFIX19. Plasmid borne kanamycin is not part of the final vector but may be present as a residual impurity. The level of residual plasmid DNA is reduced during purification but it is not possible to remove it completely therefore where levels exceed <100pgAPH[7]/$10^9$ viral genomes, the batch of AAV8-hFIX19 is rejected. Residual plasmid DNA containing the gene for kanamycin resistance may therefore be administered to patients. There is a risk of horizontal transmission of residual levels of the kanamycin resistance

[7] APH = aminoglycoside phosphotransferase which confers kanamycin resistence.

gene to bacteria however according to the notifier this risk is very low since the residual plasmid DNA is present only transiently being quickly cleared from the body and the bacteria would need to actively and simultaneously infect the tissues where the residual plasmid DNA is present.

**Risks to the Environment**

Wild type AAV is not known to be involved in environmental processes. It does not respire and does not contribute to primary production or decomposition processes.

There are no known natural predators, preys, parasites, competitors or symbionts associated with wild type AAV. Primate (human) AAV serotypes are not known to actively transfer genetic material to organisms other than primates under natural conditions, although an absence of zoonosis is not documented.

It survives in the environment as a persistent latent infection in the host vertebrate species or as a latent infection in the nucleus of some infected cells where it may remain inactive indefinitely or be reactivated giving rise to secretion of virus.

Outside of the host, AAV is resistant to low level disinfectants, is capable of surviving outside the laboratory environment and can easily be transmitted via fomites[8]. AAV particles are resistant to a wide pH range (pH 3-9) and can resist heat at 56°C for 1 hour. AAV does not form survival structures but can remain infectious for at least a month at room temperature following simple dessication or lyophilisation.

The modification described is not expected to have any effect on the host range, stability or survival of the GMO when compared to that of the wild-type virus. However, the modified organism (AAV8-hFIX19) is unable to replicate independently, even in the presence of a helper virus, since it lacks the *rep* and *cap* genes required for rescue/packaging. Therefore, the presence of the expression cassette is expected to confer a severe selective disadvantage to the GMO. AAV8-hFIXIX is not anticipated to have any direct effects on the environment (other than humans).

Therefore, based on the nature of the GMO, the parental organism and the receiving environment, the deliberate release of AAV8-hFIX19 is not anticipated to have any direct effects on the environment (other than humans).

| Storage, preparation and administration of the vector |
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The proposed deliberate release will be performed at the National Centre for Hereditary Coagulation Disorders, St James's Hospital, James's Street, Dublin 8.

[8] Fomites – inanimate objects (towel, money, clothing) that can transmit infectious agents from one individual to another.

AAV8-hFIX19 vector will be taken in from the United States and provided to the St James's Hospital site on a subject-by-subject basis, further to confirmation of patient eligibility

A pharmacist will be responsible for receipt of the vector, its storage prior to use, preparation on the day of administration and subsequent disposal. He/she will also be responsible for documentation tracing, storage / use / disposal of the vector.

AAV8-hFIX19 vector will be supplied as a frozen liquid and will be stored in a -60°C freezer within the St James's Hospital site. Since the recombinant vector will be supplied on demand, it is unlikely that it will be stored for more than one month prior to administration. The recombinant vector will be prepared in a Microbiological Safety Cabinet to reduce the risks posed by the possibility of generating and inhaling aerosols, as well as to protect the vector from contamination. The vector will be thawed, diluted in normal saline containing human serum albumin at a final concentration of 0.25% and in a volume of 200mL. Once prepared, the dose (contained in an infusion bag) will be labelled, double bagged and taken to the medical facility in a designated container (with a biohazard symbol) for patient administration.

AAV8-hFIX19 vector will be administered to 3 – 6 consenting adult males with severe Haemophilia B. Administration will be a single intravenous infusion performed by a medical professional. Eligible patients will be admitted to the hospital on the day of AAV8-hFIX19 infusion. The AAV8-hFIX19 vector will be infused through a catheter over one hour. On completion of the infusion, the catheter will be flushed with saline and will be removed approximately 20 ± 4 hours after the infusion. Patients will remain in-hospital for approximately 24 hours of observation to monitor for adverse effects related to the procedure.

## Worker protection measures taken during the release

Administration of the recombinant vector will be performed by a medical professional. According to the notifier, no other precautions are required to administer the vector other than to wear disposable gloves. However, conditions 5.2 and 6.1 require the implementation of SOPs relating to the handling of the GMO within the medical facility and worker protection measures respectively.

## Waste treatment

Following administration of AAV8-hFIX19 at the medical facility, used (or partially used) vials of vector/ empty capsids[9], syringes used in dose preparation, infusion bags and infusion sets are retained and stored in a labelled biohazard bag in the pharmacy at below -60°C for a period of no less than two months, for further investigation, should the need arise. Where such an investigation is triggered by, for example, an unexpected adverse event in a patient, these stored materials will be shipped back to the US (in accordance

[9] A capsid is the protein shell that surrounds a virus particle

with IATA shipping guidelines) in order to rule out any product defect, such as presence of excessive impurities or possible contamination of the GMO product administered.

Condition 7.3 deals with the retention of these items and requires that they are double bagged, sealed, labelled appropriately, stored in an ultra-low temperature freezer and the Agency notified of the location of the freezer within the medical facility. Condition 8.4 dealing with the notification of accidents / incidents to the Agency also requires that the Agency be notified of any instance where the GMO contaminated materials retained for further investigation become the subject of such an investigation.

Following the minimum two month retention period, the abovementioned waste will be secured in sealed bags, and in the event that no investigation is warranted, may be decontaminated on-site (condition 7.4), collected by SRCL Ltd. (GMO Register No G0163) for decontamination by SRCL Ltd or for exportation for incineration (condition 7.5).

Disposable sharps material will be collected in a sharps bin which will be sealed when full and collected for treatment and disposal by SRCL Ltd. Disposable GMO contaminated solid waste (gloves, tissue, plastic pipettes etc) is routinely autoclaved on-site in St James's Hospital at 126°C for 30 minutes, 2.4 bar.

Disinfecting agents used to decontaminate non-disposable equipment which may potentially be contaminated, surfaces of the Microbiological Safety Cabinet etc include:

- sodium hypochlorite (1 – 10%);
- alkaline solutions at pH>9;
- 5% phenol.

Alternatively, non-disposable equipment / materials may be autoclaved in St James's Hospital at 134°C for 3 minutes, 3.2 bar.

## Duration and frequency of monitoring

Patients will be monitored throughout treatment by the Principal Investigator and clinical trial staff. Any serious adverse event will be reported to the notifier.

Patients will remain in hospital for approximately 24 hours of observation to monitor for adverse effects relating to the procedure. A series of tests, largely comprising blood tests, will be conducted at regular intervals to assess safety throughout the first year following administration. Safety tests will include PCR[10] testing for vector shedding in saliva, blood and urine at each weekly visit until week 12 (or until 2 consecutive samples are negative). PCR testing of semen will be performed at each monthly visit until 2 consecutive samples are negative. Factor IX activity/antigen will be monitored weekly until week 12, and monthly thereafter until month 12.

[10] PCR – Polymerase Chain Reaction – a method to sequence DNA.

Thereafter patients will also be subject to long term follow-up over 15 years. Laboratory tests for safety and FIX activity will be performed in years 2 – 5.
For the subsequent ten years, subjects will be contacted at a minimum of once per year for the purposes of completing a clinical questionnaire. The target organ, the liver, will undergo ultrasound every three years.

## 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. The notice was published in "The Echo" newspaper (circulating in the area of St James's Hospital) on 21 February 2013, and the period for submission of representations ended on 20 March 2013. The Agency received no representations during this period.

## Review of the notification by the EPA and external consultation

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

### External Review

#### *View of the GMO Advisory Committee*

The GMO Advisory Committee

The Agency held a meeting of the GMO Advisory Committee (GMO AC) on the 7th March 2013. During this meeting committee members were given full access to confidential information submitted in connection with this application which was subsequently discussed.

There was general agreement among Advisory Committee members that the Agency should seek the opinion of a Virologist with particular emphasis on:

- The potential of the viral vector to undergo recombination;
- The capability of the viral vector to persist in the recombined state; and
- any consequences arising therefrom.

The Agency in turn sought the opinion of Professor Greg Atkins, who is an expert in the area of viral vectors and a member of the Agency's GMO Advisory Committee.

Professor Atkins' report is provided in Appendix 1. He acknowledged that there was a small chance that wild type AAV could be generated from the vector by an unlikely recombination event in the infected cell or in the manufacturing process. However, he indicated that this would not pose a danger either for the recipients or unintended recipients since the expression vector has a large portion of the AAV genome deleted and consequently cannot replicate in unintended recipients Factor 9 is a normal human protein and so would pose no risk.

He concluded that the GMO has negligible environmental risk, will have no adverse effects on human or animal health and that the Agency should give

consent. He did not identify any particular conditions that the Agency should impose or any particular monitoring that should be carried out by the applicant.

The GMO AC also indicated that the application did not include data from any preceding animal trials and it was queried whether any animal trials had in fact been done.

Agency response

A number of preceding animal studies were performed in particular in relation to the potential for AAV vectors to integrate into the genome of transduced cells and the potential for germline transmission to occur. These studies were referenced in the ERA part of the application and the corresponding references provided electronically.

***Consultation with other regulatory bodies and government departments***

The Agency also informed the Irish Medicines Board (IMB) of the proposed deliberate release. The IMB in turn indicated that an application in respect of the proposed clinical trial had not been received.

***Other EU member states***

As previously stated the Agency submitted the Summary Information Notification Format (SNIF) to the Commission. The Commission published the SNIF to all other EU member states for comment. The Agency did not receive any comments or observations from other member states.

**Internal review**

The EPA has reviewed the notification and the additional information.

## Conclusions

After examining the notification supplied in the notification under Article 14 of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 and the further information provided by the notifier in response to a request from the Agency under article 19(1), OCLRR conclude that this notification is in compliance with the aforementioned Regulations.

The GMO, AAV8-hFIX19 vector, expresses the gene for human coagulation factor IX (hFIX) for the treatment of patients with severe Haemophilia B (Factor IX deficiency). The objective of this clinical trial is to evaluate the safety of the GMO.

AAV8-hFIX19 is unable to replicate independently, even in the presence of a helper virus, since it lacks the *rep* and *cap* genes required for rescue/packaging.

The potential for environmental impact of the interactions between the GMO and humans is negligible.

Homologous recombination between AAV8-hFIX19 and a wild type AAV could occur if both were present in the same cell in the presence of a helper virus (triple infection). However, such recombination could only result in the exchange of the hFIX expression cassette with the *rep* and *cap* genes of the wild type virus. It is

not possible for the AAV genome to contain both *rep/cap* genes and the transgene, as this is beyond the packaging limit of the virion.

The GMO will be administered intravenously to eligible patients by medical professionals in St James's Hospital. Shedding of infective virus from treated individuals is expected to be low level and transient.

The potential effects in humans are limited to the transmission of AAV8-hFIX19 to an unintended human recipient. Any inadvertent exposure will be self-limiting, since AAV8-hFIX19 is unable to replicate independently, even in the presence of a helper virus, as it lacks the *rep* and *cap* genes required for rescue/packaging.

For those unintended individuals that may be exposed to AAV8-hFIX19, the potential adverse effects are expected to be of a lower severity than those expected in patients receiving considerably higher doses (immune response, potential for insertional mutagenesis and potential for germline transmission), and of no greater severity than wild type AAV, which is not known to be pathogenic.

## 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) has been paid in respect of a notification for a proposed deliberate release for purposes other than placing on the market.

## Recommendation

I am satisfied that on the basis of the review carried out and in particular, on the basis of the expert opinion that the risks posed to the environment and human health (general population) by the deliberate release of this GMO are negligible.

On this basis I recommend that consent be granted to The Center for Cellular and Molecular Therapeutics (CCMT) at the Children's Hospital of Philadelphia to conduct a clinical trial under Part B of the GMO (Deliberate Release) Regulations to test the safety of recombinant vector AAV8-hFIX19 at St James's Hospital, James's Street, Dublin from the date of grant of consent conditions by the Agency to 30 September 2015 subject to the conditions set out in the attached draft Consent Conditions.

Signed: _____ Date: 19/6/2013

Bernie Murray
*Inspector*
*Office of Climate Licensing & Resource Use*

## APPENDIX 1: Expert opinion of Professor Greg Atkins

**Application for the proposed deliberate release of a GMO (G0498-01)**

This is an important application for a Phase I/II clinical trial for the treatment of haemophilia B with an adeno-associated virus (AAV) vector expressing human factor IX. Between 4-8 Irish patients will be used and it is intended to carry out parallel studies in Australia and the USA. The principal investigators are well qualified and highly experienced.

Wild-type AAV is present as a persistent infection in the human population and antibodies are widespread. It is, however, non-pathogenic and classified in category I by the EU, which includes microorganisms unlikely to be pathogenic for man or animals. However, level II will be used in this trial as a precaution. There is a small chance that wild-type AAV could be generated from the vector by an unlikely recombination event in the infected cell or in the manufacturing process. However this would not pose a danger either for the recipients or unintended recipients. The expression vector has a large portion of the AAV genome deleted and so cannot replicate in unintended recipients. Factor 9 is a normal human protein and so would not pose a risk.

Here are the answers to your questions:

1. Is the GMO safe?
This GMO has negligible risk.

2. Is the GMO, likely to cause an adverse effect

a. on the environment
This GMO has negligible environmental risk associated with it.

b. on human and/or animal health
(whether direct or indirect, immediate or delayed) e.g. the spread of the GMO in the environment through shedding, through recombination or the uptake of genetic material from other organisms?

This GMO will have no adverse effect on human or animal health.

3. In your opinion, is the Risk Assessment satisfactory?
The risk assessment is logical and well written

4. Should the Agency give or refuse consent?
The Agency should give consent.

In the event that the Agency gives consent

a. are there any particular conditions the Agency should impose?
No

or,

b. is there any particular monitoring that should be carried out by the applicant?
No.