Headquarters
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Ireland

Consent to a deliberate release of a GMO into the environment for purposes other than for placing on the market

[SNIF No: B/IE/13/01]

GMO Register Number:	**G0498-01**
GMO Notifier:	The Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia
Address of Notifier:	5th Floor Colket Translational Research Building 3501 Civic Center Boulevard Philadelphia PA 19104-4319 USA
GMO Notifier's legal Representative in the EU	Alan Boyd Consultants Ltd (UK) Electra House Crewe Business Park Crewe CW1 6GL United Kingdom

Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003)

Consent to a deliberate release of a GMO into the environment for purposes other than for placing on the market

Decision of the Agency, under Article 18(5)(a) of the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003).

SNIF Reference No: B/IE/13/01

Register of Genetically Modified Organisms (GMOs) Users in Ireland: G0498-01

The Agency in exercise of the powers conferred on it by the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003) hereby grants consent to:

The Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia
5th Floor Colket Translational Research Building
3501 Civic Center Boulevard
Philadelphia, PA 19104-4319
USA

to carry out the following activity:

A deliberate release into the environment of recombinant hybrid Adeno-Associated Virus (AAV) which has been engineered to express human coagulation factor IX (AAV8-hFIX19), for purposes other than for placing on the market in the following location:

National Centre for Hereditary Coagulation Disorders
St James's Hospital
James's Street
Dublin 8

The period of release extends from the date of grant of these consent conditions to 30 September 2015.

SEALED by the Seal of the Agency on this the 3rd day of July 2013

PRESENT when the seal of the Agency was affixed hereto:

Frank Clinton
Authorised Person

DECISION

The Agency, in exercise of the powers conferred on it by the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003) for the reasons hereinafter set out, grants this consent to:

The Center for Cellular and Molecular Therapeutics at the Children's Hospital of Philadelphia
5th Floor Colket Translational Research Building
3501 Civic Center Boulevard
Philadelphia, PA 19104-4319
USA

to carry on the deliberate release into the environment for purposes other than for placing on the market in the following location:

National Centre for Hereditary Coagulation Disorders
St James's Hospital
James's Street
Dublin 8

subject to nine conditions as set out in the conditions/annexes attached hereto.

REASONS FOR THE DECISION

The Agency is satisfied on the basis of the information provided that, subject to compliance with the conditions of this consent, the notifer will ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment. Furthermore, the Agency believes that the risk to human health and the environment from the deliberate release of this GMO is negligible.

In arriving at its decision, the Agency considered the following aspects:

i. *the patient receiving the treatment insofar as they are part of the general population and the wider environment;*

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

iii. *potential environmental concerns.*

The Agency did not consider the risks that the treatment might pose for the patient as an individual volunteering to participate in the trial.

In reaching this decision, the Agency has considered the notification and supporting documentation received in respect of the notification, and the report of its inspector.

The consent is granted in accordance with Article 18(5)(a) of the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003).

INTERPRETATION

Agency	The Environmental Protection Agency (EPA)
Competent Authority	The Environmental Protection Agency is the Competent Authority for the purposes of the GMO (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003).
Consent	Consent issued in accordance with Article 18(5) of the GMO (Deliberate Release) Regulations, 2003, (S.I. No. 500 of 2003)
Deliberate Release	Means any intentional introduction into the environment of a genetically modified organism or a combination of genetically modified organisms for which no specific containment measures are used to limit their contact with, and to provide a high level of safety for, the general population and the environment, and cognate words and expressions shall be construed accordingly.
Directive	Means Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.
Environmental Risk Assessment	Means an evaluation, carried out in accordance with the Second Schedule, of risks to human health or the environment, whether direct or indirect, immediate or delayed, which the deliberate release or the placing on the market of a genetically modified organism may pose.
GMO	Genetically Modified Organism means an organism, other than a human being, in which the genetic material has been altered in a way that does not occur naturally by mating or natural recombination or by a combination of both. For the purposes of this trial, the GMO 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). The GMO is denoted as AAV8-hFIX19.
GMO Register	A register of GMO users in Ireland, which is available for inspection at Agency Headquarters by any person during office hours. The register

	provides details of both deliberate release and contained use of GMOs in Ireland.
GMO Regulations	Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. 500 of 2003)
Micro-organism	Micro-organism means any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture.
Notification	A notification means the submission of required information to the competent authority.
Notifier	Means any legal or natural person submitting a notification or, where the context so requires, any legal or natural person responsible for a deliberate release or for a placing on the market, or for meeting any other requirement of the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 in relation to a deliberate release or a placing on the market.
Obligation	A person who carries out a deliberate release or placing on the market shall ensure that all appropriate measures are taken to avoid adverse effects on human health or the environment arising from the deliberate release or placing on the market. Without prejudice to any other provision of the GMO Regulations, a person who proposes to submit a notification for consent in accordance with Part II of the GMO Regulations to deliberately release a GMO or in accordance with Part III of the GMO Regulations to place a GMO on the market shall, prior to submitting the said notification, carry out an environmental risk assessment in accordance with the Second Schedule of the GMO Regulations. In making an environmental risk assessment, the person proposing to carry out the deliberate release or placing on the market shall give particular attention to the risks to human health or the environment posed by the deliberate release or the placing on the market of a genetically modified organism which contains one or more genes expressing resistance to antibiotics used in human or veterinary medicine.
Organism	Has the meaning given to it in Section 111 of the Environmental Protection Agency Acts (1992 to

	2011) and includes any biological entity capable of replication or transferring genetic material.
Principal Investigator	The principal investigator at the National Centre for Hereditary Coagulation Disorders, St James's Hospital, James's Street, Dublin 8, as reported to the Agency by the notifier.
Relevant Hospital Staff	Means the Principal Investigator and other delegates, the Health and Safety Co-ordinator at the hospital and the Chief Executive Officer of the hospital.
SOPs	Standard Operating Procedures

Consent Conditions for GMO Register Entry No: G0498-01

Condition 1 Scope

1.1 This consent is for the purposes of compliance with the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 (S.I. No. 500 of 2003) only, in relation to the carrying out of deliberate release trials (clinical trials) as specified in Condition 2.

1.2 Nothing in this consent shall be construed as negating the statutory obligations or requirements of the notifier under any other enactments or regulations.

1.3 No modifications to the deliberate release, as described in the notification and supporting information submitted to the Agency, shall take place without written approval of the Agency.

Reason: To clarify the scope of the consent

Condition 2 Duration and Location of the Clinical Trial

2.1 This consent is for the purposes of conducting a clinical trial at the following hospital from the date of grant of these consent conditions to 30th September 2015:

National Centre for Hereditary Coagulation Disorders
St James's Hospital
James's Street
Dublin 8

Reason: To clarify the duration and location of the clinical trial

Condition 3 Management of the clinical trial

3.1 The notifier shall employ a suitably qualified and experienced person who shall be designated as the person in charge, i.e. the Principal Investigator (PI). The name of this PI shall be submitted to the Agency, and made known to Relevant Hospital Staff, at least one month prior to the commencement of the clinical trial. Any change to this designation during the course of the trial shall be notified immediately to both the Agency and the Relevant Hospital Staff.

3.2 The notifier, through the PI, shall ensure that personnel involved in performing specifically assigned tasks shall be:

3.2.1 suitably qualified in terms of appropriate education, training and experience as required;

3.2.2 issued with a copy of the consent conditions prior to the commencement of the trial.

3.3 The PI shall also be responsible for the implementation of SOPs referred to under Condition 5.2.

Reason:	**To make provision for management of the activity on a planned basis having regard to the desirability of ongoing assessment, recording and reporting of matters affecting the environment**

Condition 4 Duty of the notifier to inform the Agency of new information

4.1 If, following the granting of this consent, new information relevant to the deliberate release becomes available, or there is an unintended change to the deliberate release which could have consequences for the risks to human health or the environment, the notifier, through the PI, shall:

4.1.1 immediately take the necessary measures to protect human health and the environment;
4.1.2 inform the Agency as soon as the new information becomes available or the unintended change is known;
4.1.3 inform the Agency as soon as possible of such further measures the notifier in conjunction with the PI has taken or proposes to take in relation to the matters concerned.

4.2 The Agency may, following an evaluation of the matters concerned, require the notifier, in writing to:

4.2.1 modify the conditions; or,
4.2.2 suspend or terminate the deliberate release.

4.3 In the event that the Agency suspends the deliberate release further to evaluation of the new information/unintended change, the deliberate release activity shall not resume until such time as the notifier obtains written consent from the Agency permitting its recommencement.

Reason:	**To provide and update information on the clinical trial**

Condition 5 Containment measures to be used at the Deliberate Release Site

5.1 In order to keep the exposure of humans and the environment to the GMO to the lowest practicable level and to ensure a high level of safety, the PI shall apply:

5.1.1. the general principles of Good Microbiological Practice and of Good Occupational Safety and Hygiene (*Annex II*);
5.1.2. the containment measures set out in Table IA of the Fourth Schedule of the GMO (Contained Use) Regulations (2001 to 2010) (*Annex III*), which correspond to the class of the contained use, i.e. containment level 1 measures, including '*optional* measures.

5.2 Standard Operating Procedures (SOPs)

5.2.1 In order to ensure the safety of personnel working in the facility, the PI shall, prior to the date of commencement of the deliberate release, implement appropriate SOPs on the following:

- Training of staff with responsibilities relating to the GMO during the clinical trial;
- Receipt of the GMO at the location of the clinical trial;
- Secure storage of the GMO within the medical facility;
- Transport, movement and handling of the GMO within the medical facility;
- Preparation and administration of the GMO;
- Treatment of GMO spillages with disinfectants;
- Cleaning and disinfection of non-disposable equipment;
- Operation, testing and maintenance of containment equipment;
- Measures for limiting access to the medical facility;
- Treatment of GMO waste;
- Maintenance of records relating to staff training, inactivation events and the storage of GMO stocks/GMO contaminated waste material;
- Worker protection measures to be taken during the release.

5.2.2 The PI shall submit copies of these SOPs to the Agency for approval at least two weeks prior to commencement of the clinical trial. The agreed SOPs shall be made available to all Relevant Hospital Staff at least one week prior to commencement of the trial.

Reason:	**To ensure proper management of the clinical trial and to avoid adverse effects on human health and the environment arising from the clinical trial**

Condition 6 Worker Protection Measures to be taken during the clinical trial

6.1 The notifier, through the PI, shall implement worker protection measures during the clinical trial. These measures shall apply to all staff involved in the execution of the clinical trial. An SOP setting out these worker protection measures and how they will be implemented shall be made available to clinical trial staff prior to trial commencement. This SOP shall be made available to the Agency upon request.

Reason:	**To comply with the legislation and to avoid adverse effects on human health and the environment**

Condition 7 Waste Management

7.1 Disposable materials contaminated with the GMO must be inactivated by validated means before disposal. This inactivation shall take place on the same site as the use of the GMO, unless otherwise agreed by the Agency.

7.2 All un-used GMO material shall be inactivated by validated means prior to disposal. This inactivation shall take place on the same site as the use of the GMO, unless otherwise agreed by the Agency.

7.3 Contaminated materials to be retained for further investigation subsequent to administration of the GMO, shall be double bagged, sealed, labelled 'GMO contaminated' with details of the GMO and date and stored separately in an 'ultra-low temperature freezer'. The Agency shall be notified of the precise location of this freezer within the medical facility prior to trial commencement.

7.4 On–site inactivation

7.4.1 On-site inactivation methods may comprise chemical inactivation and/or autoclaving. The chosen method of inactivation must be validated under normal working conditions. A copy of the validation protocol and validation results must be retained by the PI and made available to the Agency on request.

7.4.2 In accordance with the Principles of Good Microbiological Practice and Good Occupational Safety & Hygiene (*Annex II*), control measures must be applied at least monthly to ensure that inactivation methods remain adequate and effective. Records (e.g. logbook) must be retained by the notifier for inspection by the Agency on request.

7.4.3 Records of GMO inactivation events (e.g. autoclave printouts, logbooks) shall be maintained by the PI and shall be made available for inspection by the Agency on request.

7.5 Off-site inactivation

7.5.1 Where the on-site inactivation of the GMO is not feasible, the GMO shall be sent to an off-site inactivation facility, with the prior agreement of the Agency.

7.5.2 The agreed facility shall be registered and regulated in accordance with the Genetically Modified Organisms (Contained Use) Regulations 2001 to 2010, or shall comply with the provisions of the appropriate National and European legislation and protocols.

7.5.3 Records of off-site GMO waste inactivation must be obtained from the waste contractor and retained by the PI for inspection by the Agency on request.

Reason:	**To ensure proper management of un-used GMO material and GMO wastes so as to avoid adverse effects on human health and the environment**

Condition 8 Record Keeping and Reporting to the Agency

8.1 Record keeping and reporting to the Agency shall be in accordance with Annex I.

8.2 The notifier, through the PI, shall inform the Agency of the date of commencement of the clinical trial no later than 1 week prior to its commencement.

8.3 The notifier, in conjunction with the PI, shall keep accurate records of:

8.3.1 the batch numbers (if applicable) and corresponding quantities of GMO received, stored, prescribed and used/dispensed during the course of the clinical trial;
8.3.2 the name of each patient taking part in the trial;
8.3.3 the date on which the GMO is administered to the patient and the dosage administered.

These records shall be made available to the Agency on request.

8.4 Further to the administration of the GMO to the patient, the notifier, through the PI, shall keep a record of the following for each patient:

8.4.1 the monitoring performed; and,
8.4.2 the results of the monitoring carried out.

These records shall be made available to the Agency on request.

8.5 Any unforeseen accidents or incidents involving the GMO, including where GMO contaminated materials retained for further investigation become the subject of such an investigation, shall be notified to the Agency and the Relevant Hospital Staff. Where the Agency deems necessary the notifier, in conjunction with the PI, shall submit a report to the Agency within one week of such an accident / incident, setting out the actions taken in response to the accident / incident, to minimise the risk of exposure to the GMO. This report shall also be made available to Relevant Hospital Staff.

Where GMO contaminated material retained for further investigation becomes the subject of further investigation, the Agency shall be informed of the outcome of that investigation.

8.6 The PI, shall maintain records in respect of the following:

8.6.1 The nature and extent of GMO waste stored for purposes of further investigation, the date of storage, the date and location of decontamination (on-site or off-site).
8.6.2 On-site GMO inactivation events;
8.6.3 The movement of GM waste by SRCL Ltd (GMO Register No G0163-01) or other registered contractor for inactivation by validated means as outlined under condition 7.4;
8.6.4 all accidents/incidents relating to the use of the GMO incurred by staff members and / or patients.

These records shall be made available to the Agency on request.

8.7 Reports to the Agency on the results of the clinical trial

8.7.1 The notifier shall submit a report to the Agency, in the format set out under Commission Decision 2003/701/EC[1], (adapted for the release of a human medicinal product) on or before the 31 March 2016. This report shall include the following information:

8.7.1.1 the results of the deliberate release;
8.7.1.2 a post-release evaluation of the risks to human health and the environment; and,
8.7.1.3 where appropriate, a statement on the results of the clinical trial in relation to any product, or type of product, in respect of which consent to placing on the market may be sought.

8.8 On completion of the clinical trial, the notifier shall notify the Agency in writing. The Agency shall indicate how any residual GMO material has been destroyed and disposed of.

8.9 Training records signed by all staff in receipt of training relating to the GMO deliberate release activity, shall be approved and maintained by the PI. These records shall be made available to the Agency on request.

Reason:	**To maintain written records of the clinical trial and make provision for the reporting to the Agency of any impacts of the completed clinical trial and associated risks**

Condition 9 Charges

9.1 The notifier shall pay the Environmental Protection Agency €1,226 in total which shall be paid within three months of date of the issue of this consent.

Reason:	**To provide for the performance of a site inspection and the consultant fees for an expert opinion**

[1] Commission Decision of 29 September 2003 establishing pursuant to Directive 2001/18/EC of the European Parliament and of the Council a format for presenting the results of the deliberate release into the environment of genetically modified higher plants for purposes other than placing on the market (*notified under document under C(2003) 3405*) (2003/701/EC)

Annex I

SCHEDULE OF REPORTING / MAKING INFORMATION AVAILABLE

Deadline	**Information to be submitted to the EPA**	**Information to be made available to clinical trial staff**
to be provided **1 month** prior to trial commencement	The notifier shall provide the name of the PI and his/her contact details (i.e. telephone number, mobile number and e-mail address)	
to be provided **2 weeks** prior to trial commencement	The PI shall provide copies of SOPs set out under condition 5.2.1 for approval	
to be provided **1 week** prior to trial commencement	Notifier/PI Date of trial commencement	Notifier/PI shall make available to clinical trial staff: • Consent conditions issued by the EPA; • SOPs set out under condition 5.2.1.
to be provided prior to trial commencement	PI Location of ultra-low temperature freezer	**PI** • shall implement SOPs set out under condition 5.2.1. • make SOP on worker protection measures (Condition 6) available to clinical trial staff
to be provided on request	SOP on work protection measures (condition 6.1)	
	Validation protocol / results for on-site inactivation procedures (condition 7.4.1)	
	Records of on-site GMO inactivation events (condition 7.4.3 / 8.5.2)	
	On-site GMO inactivation control measures applied (condition 7.4.2)	

	Off-site inactivation of GMO waste (condition 7.4.3 /8.5.3)	
	Receipt, storage of GMO, patient details including dosage (condition 8.2)	
	Monitoring (condition 8.3)	
	Waste storage records (condition 8.5.1)	
	Accidents/incidents (condition 8.5.4)	
	Training records (condition 8.8)	
to be provided on trial completion	Notifier • Notification of trial completion • Destruction/disposal of residual GMO material • Report in the format set out under Commission Decision 2003/701/EC	

Annex II

Principles of good microbiological practice and good occupational safety and hygiene practice shall include:

(i) keeping the workplace and environmental exposure to any genetically modified micro-organism to the lowest practicable level;

(ii) exercising engineering control measures at source and where necessary supplementing these with appropriate personal protective clothing and equipment;

(iii) testing and maintaining control measures and equipment;

(iv) testing where necessary for the presence of viable process organisms outside the primary physical containment;

(v) providing appropriate training of personnel;

(vi) establishing biological safety committees or subcommittees where required;

(vii) formulating and implementing local codes of practice for the safety of personnel where required;

(viii) where appropriate displaying biohazard signs;

(ix) providing washing and decontamination facilities for personnel;

(x) keeping adequate records;

(xi) prohibiting eating, drinking, smoking, applying cosmetics or the storing of food for human consumption in the work area;

(xii) prohibiting mouth pipetting;

(xiii) where appropriate, providing written standard operating procedures to ensure safety;

(xiv) having effective disinfectants and specified disinfection procedures available in the case of spillage of genetically modified micro-organisms and;

(xv) where appropriate, providing safe storage for contaminated laboratory equipment and materials.

Annex III

Table IA

Containment measures for contained use of genetically modified micro-organisms in a laboratory

Measures		**Containment levels**			
		1	2	3	4
1	Laboratory Suite	Not required	Not required	Required	Required
2	Laboratory: sealable for fumigation	Not required	Not required	Required	Required
Equipment					
3	Surfaces resistant to water, acids, alkalis, solvents, disinfectants, decontamination agents and easy to clean	Required for bench	Required for bench	Required for bench and floor	Required for bench, floor, ceiling and walls
4	Entry to laboratory via airlock	Not required	Not required	Optional	Required
5	Negative pressure relative to the pressure of the immediate environment	Not required	Not required	Required	Required
6	Extract and input air from the laboratory should be HEPA-filtered	Not required	Not required	Required	Required for input and extract air
7	Microbiological safety cabinet	Not required	Optional	Required	Required
8	Autoclave	On site	In the building	En suite	Double-ended autoclave in laboratory
System of work					
9	Restricted access	Not required	Required	Required	Required
10	Biohazard sign on the door	Not required	Required	Required	Required
11	Specific measures to control aerosol dissemination	Not required	Required to minimise	Required to prevent	Required to prevent
12	Shower	Not required	Not required	Optional	Required
13	Protective Clothing	Suitable protective clothing	Suitable protective clothing; footwear optional	Suitable protective clothing and footwear	Complete change of clothing and footwear before

					entry and exit
14	Gloves	Not required	Optional	Required	Required
15	Efficient vector control (e.g. for rodents and insects)	Optional	Required	Required	Required
Measures		**Containment levels**			
		1	2	3	4
Waste					
16	Inactivation of genetically modified micro-organisms in effluent from hand-washing sinks or drains and showers and similar effluents	Not required	Not required	Optional	Required
17	Inactivation of genetically modified micro-organisms in contaminated material and waste	Optional	Required	Required	Required
Other Measures					
18	Laboratory to contain its own equipment	Not required	Not required	Optional	Optional
19	Observation window or alternative to enable occupants to be seen	Optional	Optional	Optional	Required

For the purpose of this Table:

(1) In measure 1, "*isolation*" means that the laboratory is separated from other areas in the same building or is in a separate building

(2) In measure 4, "*airlock*" means that the entry must be made through a chamber isolated from the laboratory. The clean side of the airlock must be separated from the restricted side by changing or showering facilities, or by interlocking doors.

(3) In measure 5, "*negative pressure relative to the pressure of the immediate environment*" is only required for a class 3 contained use where airborne transmission can occur.

(4) "*HEPA*" means high efficiency particulate air.

(5) In measure 6, where viruses which are not capable of being retained by HEPA filters are used in class 4 contained use, extra requirements shall be provided for extract air.

(6) In measure 8, "en suite" means that where the autoclave is located outside the laboratory in which the contained use is being carried out but within the laboratory suite, validated procedures shall be in place to ensure the safe transfer of material into the autoclave and to provide a level of protection equivalent to that which would be achieved if the autoclave were in the laboratory.

Sealed by the seal of the Agency on this the 3rd day of July 2013.

PRESENT when the seal of the Agency was affixed hereto:

Frank Clinton
Authorised Person