Headquarters
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Ireland

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

[SNIF No: B/IE/10/362]

GMO Register Number: **G0362-01**

GMO Notifier: **Applied Genetics Technologies Corporation**
11801 Research Drive, Suite D
Alachua, FL 32615
United States of America

Address of Notifier: **11801 Research Drive, Suite D,**
Alachua, FL 32615,
United States of America

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

Consent to a deliberate release of a GMM 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/10/362

Register of Genetically Modified Organisms (GMOs) Users in Ireland: G0362-01

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:

Applied Genetics Technologies Corporation
11801 Research Drive, Suite D
Alachua, FL 32615
United States of America

to carry out the following activity:

A deliberate release into the environment of a Genetically Modified Micro-organism (GMM), a gene therapy product named *rAAV1-CB-hAAT (a recombinant adeno-associated virus (AAV) which has been engineered to express human alpha-1 antitrypsin)*, for purposes other than for placing on the market in the following location:

- Beaumont Hospital, Beaumont Road, Dublin 9, Ireland

The period of release extends from 11th August 2010 to 31st July 2011

SEALED by the Seal of the Agency on this the
11th day of August 2010

PRESENT when the seal of the Agency
was affixed hereto:

Laura Burke
Director/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:

Applied Genetics Technologies Corporation, 11801 Research Drive, Suite D, Alachua, FL 32615, United States of America

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

Beaumont Hospital, Beaumont Road, Dublin 9, Ireland

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 user 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 GMM is low.

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 GMM 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.
GMM	Genetically Modified Micro-organism means a micro-organism 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.
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 2007) and includes any biological entity capable of replication or transferring genetic material.
Principal Investigator	The principal investigator at Beaumont Hospital, Beaumont Road, Dublin 9, Ireland, as reported to the Agency by the notifier.
Relevant Hospital Staff	Means the Principal Investigator and other relevant staff mentioned in the notification, 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: G0362-01

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

1.2 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 between August 2010 and July 2011:

- *Beaumont Hospital, Beaumont Road, Dublin 9, Ireland*

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. The name of this Principal Investigator shall be submitted to the Agency, and Relevant Hospital Staff, at least two weeks in advance of 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.

3.3.1 The notifier shall ensure that personnel involved in performing specifically assigned tasks shall be qualified on the basis of appropriate education, training and experience as required and shall be aware of the requirements of the consent conditions.

3.3.2 The Principal Investigator shall also be responsible for the implementation of the SOPs as required 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 that could have consequences for the risks to human health or the environment, the notifier shall:

i. Inform the Agency as soon as the new information becomes available;
ii. Take necessary measures to protect human health and the environment; and,
iii. Inform the Agency as soon as possible of such further measures the licensee has taken or proposes to take in relation to the matters concerned.

The Agency may, following an evaluation of the matters concerned, require the notifier, in writing, to modify the conditions of, suspend or terminate the deliberate release.

Reason:	***To provide and update information on the clinical trial to be conducted at Beaumont Hospital.***

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 genetically modified micro-organisms to the lowest practicable level and to ensure a high level of safety, the notifier shall apply:

(a) the general principles of Good Microbiological Practice and of Good Occupational Safety and Hygiene (*Annex I*);

(b) the containment measures set out in Table 1A of the Fourth Schedule of the GMO (Contained Use) Regulations (S.I. 73 of 2001) (*Annex II*), which correspond to the class of the contained use, i.e. containment level 1 measures, including '*optional*' measures.

5.2 Standard Operating Procedures

5.2.1 In order to ensure the safety of personnel working in the contained use facility the notifier shall, prior to the date of commencement of the deliberate release, draw up and implement appropriate SOPs on the following:

- Training of Staff with responsibilities relating to the GMM during the clinical trial;
- Receipt of the GMM (the study product) at the release site;
- Secure storage of the GMM;
- Transport, movement and handling of GMMs within the trial site and outside the trial site, where relevant;
- Preparation of the GMM (study product);
- Intramuscular injection/Administration of the GMM;
- Treatment of GMM spillages with disinfectants;

- Cleaning and disinfection of equipment;
- Operation, testing and maintenance of containment equipment at the GMM trial sites;
- Measures for limiting access to the GMM trial sites;
- Disposal of GMM waste;
- Maintenance of records and logbooks relating to training records, inactivation events and the storage of GMM stocks;
- Emergency planning, as outlined in the notification;
- Worker protection measures to be taken during the release.

5.2.2 Copies of these SOPs shall be submitted to the Agency for approval, at least two weeks in advance of commencement of the clinical trial, and to the Relevant Hospital Staff.

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 shall implement worker protection measures during the clinical trial. These measures shall apply to all Relevant Hospital 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 sent to the Agency in accordance with Condition 5.2.

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

Condition 7 Waste Management

7.1 Contaminated disposables such as disposable lab coats, gloves, tissues, plastic pipettes, spent liquid culture and solid media waste containing viable GMMs must be inactivated by validated means before disposal. This inactivation shall take place on the same site as the use of the GMM, unless otherwise agreed by the Agency.

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

7.3 On–site inactivation

7.3.1 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 notifier and made available to the Agency on request.

7.3.2 In accordance with the Principles of Good Microbiological Practice and Good Occupational Safety & Hygiene (*Annex 1*), control measures (e.g. spore strips) must be applied at least weekly to ensure that inactivation methods remain adequate and effective. Corresponding records must be retained by the notifier for inspection by the Agency on request.

7.3.3 Records of GMM inactivation events (e.g. autoclave printouts, logbooks) shall be maintained by the notifier. These records shall be signed off by the Principal Investigator on a weekly basis and made available for inspection by the Agency on request.

7.4 Off-site inactivation

7.4.1 Where the on-site inactivation of the GM material is not feasible, the GM material shall be sent to an off-site inactivation facility with the prior agreement of the Agency. The agreed facility shall be registered and regulated in accordance with the Regulations, or shall comply with the provisions of the appropriate National and European legislation and protocols.

7.5 Records of all GMM waste inactivation must be retained by the notifier for inspection by the Agency on request.

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

Condition 8 Record Keeping and Reporting to the Agency

8.1 The notifier shall keep a record of the name of each patient and the date on which the GMM is administered to the patient. These records shall be made available for inspection by the Agency on request.

8.2 Results of monitoring for viral shedding for each patient administered with the GMM, shall be submitted to the Agency as soon as they become available.

8.3 Any spillages or other unforeseen incidents involving GMM material shall be notified immediately to the Agency and the Relevant Hospital Staff. The notifier shall submit a report to both the Agency and the Relevant Hospital Staff within one week of such an incident, setting out the actions taken in response to the incident to minimise risk of exposure to any GMM inadvertently released as a result of such an incident.

8.4 The notifier shall maintain log books in respect of the following:

- the storage of GMM stock material;
- GMM inactivation events;

- training records for members of staff associated with the GMM contained use activity;
- all accidents/incidents.

These log books shall be made available to the Agency on request.

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

8.5.1 After completion of the clinical trial, the notifier shall submit a report to the Agency. In particular the report shall include the following:

- the results of the clinical trial;
- a post-release evaluation of the risks to human health and the environment; and,
- 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.

The notifier shall have regard for Commission Decision (C(2003) 3405) when preparing the report referred to in Conditions 8.5.1 above. The report on the record of the clinical trial shall be submitted to the Agency, no later than 31st December 2011.

8.5.2 The notifier shall submit a report, each year, of the monitoring to be carried out for the subsequent four years after administration of the GMM, as described in the notification. These reports shall be submitted to the Agency no later than the 31st December each year, with the final report to be submitted no later than 31st December 2015.

8.6 In the event that the clinical trial ceases, the notifier shall inform the Agency, in writing, of such and shall indicate to the Agency how residual GMM material has been disposed of and inactivated.

8.7 A copy of the training record for staff with responsibilities relating to the GMM during the clinical trial, shall be maintained and signed by all staff who have received training and approved by the Principal Investigator. Copies shall be sent to the Health and Safety Co-ordinator at the hospital, the Chief Executive Officer at the hospital and the Agency at least two weeks prior to the commencement of the release.

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 Financial Charges for carrying out site inspections, monitoring & investigations

9.1 The notifier shall pay to the Agency an initial annual contribution of €2,733 towards the cost of monitoring the activity as the Agency considers necessary for the performance of its functions under the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 and the Environmental Protection Agency Acts 1992 to 2007. In subsequent years the notifier shall pay to the Agency such revised annual contribution as the Agency shall from time to time consider necessary to enable performance by the Agency of its relevant functions under the Genetically Modified Organisms (Deliberate Release) Regulations, 2003 and the Environmental Protection Agency Acts 1992 to 2007. All such payments shall be made within one month of the date upon which demanded by the Agency.

9.2 In the event that the frequency or extent of monitoring or other functions carried out by the Agency needs to be amended, the notifier shall contribute such sums as determined by the Agency to defray its costs in regard to items not covered by the said contribution in Condition 9.1.

Reason:	***To provide for adequate financing for monitoring and financial provisions for measures to protect the environment.***

Annex I

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 II

Table 1A

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 11th day of August 2010

PRESENT when the seal of the Agency was affixed hereto:

Laura Burke, Director/Authorised Person