OFFICE OF CLIMATE,LICENSING & RESOURCE USE

INSPECTOR'S REPORT

TO:	**BOARD OF DIRECTORS**
FROM:	Suzanne Wylde - **Environmental Licensing Programme**
DATE:	1st July 2010
RE:	**Notification from Applied Genetic Technologies Corporation, USA, under Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) to conduct a clinical trial using a genetically modified micro-organism (GMM) (GMO Register No: G0362-01).**

Applicant:	Applied Genetic Technologies Corporation, 11801 Research Drive, Suite D, Alachua, FL 32615, USA
GMO Register Entry No:	G0362-01
SNIF No:	B/IE/10/362
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 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:	30th April 2010
Request for additional information under Article 19 of S.I. 500 of 2003:	8th June 2010
Additional Information submitted under Article 19 of S.I. 500 of 2003:	23rd June 2010
Date by which decision is required:	13th August 2010
Representations to the EPA relating to this notification under Article 16 of S.I. 500 of 2003:	None to date.

Introduction

TMC Pharma Services, UK representing Applied Genetic Technologies Corporation of Alachua, Florida, USA notified the Environmental Protection Agency (Agency) on 30th April 2010 of their intent to conduct a clinical trial on patients suffering from alpha-1 antitrypsin deficiency, using a genetically modified micro-organism (GMM). The company propose to conduct this trial at Beaumont Hospital in Dublin. The notification was made in accordance with Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003)[1]. The Agency sent the Summary Notification Information Format[2] to the Commission on 14th May 2010.

If the proposal is approved by the Agency, the proposed clinical trial would also be governed by the Irish Medicines Board under the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, 2004, S.I. No 190 of 2004 and amendments.

The Agency previously issued consent to Schering Healthcare Ltd in 2002 (GMO Register No: G0134-01) to conduct a clinical trial, also using a similar GMM.

The GMM for the proposed clinical trial is a recombinant adeno-associated virus (AAV) which has been engineered to express human alpha-1 antitrypsin. The GMM is described in further detail later in this report under "*Description of the Genetically Modified Micro-Organism for use in the proposed clinical trial".*

Alpha-1 Antitrypsin is an important protein produced by the liver, which is released into the bloodstream and travels to the lungs. It protects the lungs from the destructive actions of common illnesses and exposures, particularly tobacco smoke.

Alpha-1 Antitrypsin deficiency (A1AD) is an inherited genetic disorder caused by defective production of alpha-1-antitrypsin (A1AT), thereby leading to a decreased activity of the protein in the blood and lungs. Along with Cystic Fibrosis it is the most common fatal disease in Ireland. It is estimated to affect more than 1000 people nationally[3].

There are several forms and degrees of A1AD. Severe A1AD causes panacinar emphysema[4] and/or chronic obstructive pulmonary disease (COPD)[5] in adult life in many people with the condition (especially if they

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

[2] Summary Information Notification Format (SNIF) is the form used by the European Commission for exchange of information, contained in the notification, between member states, as per Article 11 of Directive 2001/18/EC.

[3] http://www.alpha1.ie/

[4] *Panacinar* (or *panlobular*) emphysema: The entire respiratory acinus, from respiratory bronchiole to alveoli, is expanded. Occurs more commonly in the lower lobes, especially basal segments, and anterior margins of the lungs.

[5] Chronic obstructive pulmonary disease (COPD) refers to chronic bronchitis and emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation

are exposed to cigarette smoke). The deficiency can also lead to various liver diseases in a minority of children and adults. At present, treatment of the disorder involves weekly transfusions of alpha-1 antitrypsin protein, purified from plasma obtained from human donors for the lifetime of the patient, which tends to prove very costly.

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.

The remit of the Agency with regard to clinical trials is as follows:

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

It is not within the remit of the Agency to consider the risks that the treatment might pose for the patient as an individual volunteering to participate in the clinical trial. This matter falls within the remit of the Irish Medicines Board (IMB). The responsibility of the Agency relates to the wider environment and the general population. It is a matter for those conducting the trials, medical staff and health and safety personnel, to conduct their trials in a proper manner and provide for matters such as isolation of patients and care of patients, safety of staff and safe access by visitors to hospitals. This means that in assessing the notification, the Agency will be considering the potential risks to patients, staff and visitors to the hospital only insofar as they are part of the general population and the wider environment. This modus operandii has been previously agreed with the IMB.

National policy regarding the release of GMOs into the environment

The Renewed Programme for Government (10th October 2010) states:

> *"We will declare the Republic of Ireland a GM-free Zone, free from the cultivation of GM plants."*

It is clear that the document does not make reference to the use of GMOs in clinical trials.

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of the flow of air to and from the lungs causing shortness of breath. In contrast to asthma, the limitation of airflow is poorly reversible and usually gets progressively worse over time.

The use of viruses in combating human diseases

In recent times it has become apparent that some characteristics of viruses[6], which normally contribute to disease (e.g., the common cold), may be manipulated to treat disease rather than cause it. Thus viruses are being used and developed as vectors for vaccine construction, as gene therapy and as cancer therapy agents. The main viruses that have been exploited as vectors in this work so far are DNA viruses such as adeno and adeno-associated viruses and RNA viruses that synthesise a DNA copy of their genome such as retroviruses.

Gene therapy vectors based on AAV are uniquely suitable for *in vivo* gene therapy because they are non toxic, highly efficient at transducing a wide variety of non-dividing cell types, replication incompetent and persist in the target tissue for longer periods, resulting in long term expression of the transgene. Recombinant AAV vectors have been evaluated in a large number of clinical trials for a variety of diseases, including cystic fibrosis, haemophilia, Parkinson's disease and alpha-1 antitrypsin deficiency.

In this proposed clinical trial, a disabled AAV vector will be used to 'piggy back' a gene into patients to treat alpha-1 antitrypsin deficiency.

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

The GMM which is the subject of this assessment is called rAAV1-CB-hAAT, a genetically modified version of adeno-associated virus (AAV)[7]. The recombinant adeno-associated virus (rAAV) vector to be used in the clinical trial consists of a serotype 1 AAV capsid containing a DNA cassette that expresses human AAT. rAAV1-CB-hAAT is a replication incompetent, vector based on AAV serotype 1 containing cDNA encoding the human alpha-1 antitrypsin gene. rAAV1-CB-hAAT is replication incompetent due to the elimination of the *rep* and *cap* genes from its genome which have been replaced by the human alpha-1 antitrypsin gene expression cassette.

Purpose of the proposed deliberate release

The purpose of the clinical trial is to assess the efficacy and safety of rAAV1-CB-hAAT in patients with alpha-1 antitrypsin deficiency.

The Irish site in this application forms part of a multicentre clinical trial, in which rAAV1-CB-hAAT will be administered by intramuscular injection to patients with alpha-1 antitrypsin deficiency. In addition to the proposed trial in Ireland, the notifier intends to conduct two other clinical trials at selected sites in the USA.

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[6] A virus is a microorganism that contains genetic information but cannot reproduce itself. To replicate, it must invade another cell and use part of that cell's reproductive machinery

[7] Adeno-associated virus (AAV) is a small virus which infects humans and some other primate species. AAV is not currently known to cause disease and consequently the virus causes a very mild immune response. AAV can infect both dividing and non-dividing cells and may incorporate its genome into that of the host cell. These features make AAV a very attractive candidate for creating viral vectors for gene therapy.

Proposed location of the deliberate releases

The proposed location for the deliberate release is Beaumont Hospital, Beaumont Road, Dublin. It is envisaged that there will be three patients treated at Beaumont Hospital.

The Principal Investigator at Smurfit Building, Beaumont Hospital will be Professor Noel G. McElvaney. Professor McElvaney was granted consent by the Agency for the contained use of Class 1 GMMs in 2002. The laboratories of Professor McElvaney in the Smurfit Building were last inspected by the Agency, under the contained use legislation, in June 2008. The Agency was satisfied, at that time, that Professor McElvaney was in compliance with the legislation.

Timeframe for the proposed clinical trial

The notification covers the treatment of clinical trial patients at the named hospital location from July 2010 to July 2011. The investigators (doctors) at the clinical trial location will treat up to 3 patients during this time.

Confidential Information

In accordance with Article 10 of the GMO (Deliberate Release) Regulations, TMC Pharma Services representing Applied Genetic Technologies Corporation, retrospectively submitted a request to the Agency on 28th June 2010 that certain information be held confidential as it represented commercially sensitive proprietary information. The Agency approved this request on 29th June 2010 as it does not impede providing an adequate description of the GMM on the GMO register held by the Agency.

Antibiotic Marker Genes

Article 5(2)(b) of the GMO (Deliberate Release) Regulations makes reference to the obligation of the notifier to pay particular attention to the risks to human health or the environment posed by the deliberate release of an GMO containing one or more genes expressing resistance to antibiotics used in human or veterinary medicine. The GMM in question in this report contains no antibiotic marker genes.

Method(s) to be used for the release

The GMM will be administered to the patient as an intramuscular injection. A number of injections will be administered to the patient in the hospital over one day. The patient will be released following administration of the GMO but monitored at regular intervals.

The notifier informed the Agency that the product itself will be controlled under level 1 containment conditions at the study site. This will be in accordance with containment measures under the Genetically Modified Organisms (Contained Use) Regulations, 2001.

Quantities of genetically modified organisms to be released

The dosage administered to each patient participating in the trial is based on body weight. As previously mentioned, this is a multicentre trial, with three cohorts of three patients. The patients will receive dosages of rAAV1-CB-hAAT of 6 x 10^{12} vector genomes per kilogramme body weight (vg/kg) (Table 1). The number of injections administered to the patients, and thus the dosages, varies between the three cohorts. Overall patients will receive either 10, 32 or 100 injections, with the time required to administer the injections varying between 20 minutes, 1 hour or 3 hours, respectively.

Table 1: Dosages of the GMM to be administered to participating patients in the clinical trial.

Group	Route of administration[a]	Vector dose (vg/kg)	Total dose (vg per subject) [b]	Vector concentration (vg/ml) [b]	Injection number x volume
1	IM	6.0 x 10^{11}	5.4 x 10^{13}	4.00 x 10^{12}	10 x 1.35ml
2	IM	1.9 x 10^{12}	1.7 x 10^{14}	3.96 x 10^{12}	32 x 1.35ml
3	IM	6.0 x 10^{12}	5.4 x 10^{14}	4.00 x 10^{12}	100 x 1.35ml

[a] IM = Intramuscular, [b] Total vector dose and vector concentration for a 90kg subject.

Storage & Preparation of the GMM prior to release/administration

The GMM will be stored in the Smurfit Building at Beaumont Hospital prior to administration. The quantities of the GMM to be used during the clinical trial will only be ordered once the patients have been selected. The GMM dosage will be based on patient weight and as such the amount required can only be determined when suitable candidates have been selected. For this reason it is not expected that there will be any unused (*i.e.* unopened) vials of the drug product. It is not expected that the GMM will be stored for more than 2 months at Beaumont Hospital prior to administration.

The GMM will be stored in 2ml vials in a sealed container in the -80˚C freezer, segregated from other materials. Each vial will contain 1.8ml of the study agent. A maximum of 67 vials is expected to be stored at any one time. The freezer will be locked with key holders restricted to named study staff. The room in which the freezer is located is restricted by keypad access with access also restricted to named study and institutional staff.

Retention samples will be stored from each vial. These samples will be stored in the -80˚C freezer as per the storage detailed above for the duration of the trial. Once the trial has been completed these samples will be sent back to the project sponsor in the USA for archive storage. There will be no long term storage of the GMM at Beaumont Hospital.

The GMM will be prepared (diluted in a physiological buffer) in a class 2 micro-biological safety cabinet (MSC) in the laboratory complex on the ground floor of the Smurfit Building prior to administration to the patient. The MSC will be cleaned down and decontaminated thoroughly after the preparation has been completed. The MSC is validated annually by an external contractor. There are two MSC hoods in the cell culture room

where the GMM will be prepared. These were both validated last on 24th March 2010.

Worker protection measures taken during the release

The hospital staff involved in the clinical trial will receive a copy of the Study Pharmacy Manual. The Study Pharmacy Manual will include complete instructions for drug preparation and precautions for the safe and contained handling of the GMM. Such precautions will include guidance on appropriate personal protective equipment, instructions for the preparation of the work area, preparation of syringes for administration of study agent to patients and procedures for cleaning and disposal of all materials. Condition 6 of the consent conditions, as drafted, requires the notifier to implement worker protection measures during the clinical trial to apply to all relevant members of staff involved in the execution of the clinical trial.

The containment measures used will include:

- The placing of a "Biohazard" signs in areas where the GMM is being used;
- To prevent the dispersal of aerosols generated during working procedures in the working area, procedures are to be performed within a Class 2 Biological safety cabinet;
- All hospital staff involved in these studies are to be trained appropriately. Operational guidelines are to be prepared and made available to staff involved in the preparation and treatment rooms and care of patients at all times;
- The research facility is to provide protective clothing which will include goggles, face mask, gloves and gowns which are to be worn by all personnel involved in the use of the GMM.

Information about previous releases with this GMO

The proposed clinical trial in this report is a Phase 2 clinical trial. The Phase 1 clinical trial for rAAV1-CB-hAAT was conducted a number of years ago in the USA[8]. As in this case, the Phase 1 trial involved the administration of the GMM via intramuscular injection. The trial found that the vector was well tolerated. There were 9 patients in the Phase 1 trial. Three of the nine patients (those administered the highest dosage during the trial) showed an increase in AAT expression which persisted for the duration of the monitoring period (1 year).

[8] *Phase 1 trial of intramuscular injection of a recombinant adeno-associated virus serotype 2 α_1-antitrypsin (AAT) vector in AAT-deficient adults*; Brantly *et al*; Human Gene Therapy 17:1177-1186 (December 2006)

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, as well as the European Medicines Agency "*Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products"*. The risk assessment considered the following:

- Identification of any characteristics which may cause adverse effects;
- Evaluation of the potential consequences of each adverse effect, if it occurs;
- Evaluation of the likelihood of the occurrence of each identified potential adverse effect;
- Estimation of the risk posed by each identified characteristic of the GMO;
- Application of management strategies for risks from the deliberate release; and,
- Determination of the overall risk of the GMO.

The GMM in question is replication incompetent (replication genes have been deleted) and therefore is unable to colonise, to proliferate or to become invasive. The GMM has no selective advantage in any host or environment because of its inability to replicate. As such there is a negligible risk of the GMM becoming persistent under the proposed deliberate release. The potential for gene transfer to other species is low, and the likelihood of this occurring will be maintained as low by the risk management plan to be put in place by the notifier during the proposed deliberate release. Neither the GMM being considered in this notification, rAAV1-CB-hAAT, nor the wild type AAV[9] from which it is derived are considered pathogenic. There is a negligible likelihood of any immediate and/or delayed, direct or indirect environmental impacts of the GMM.

The notifier concluded in the risk assessment that, with the proposed risk management strategy in place, the overall risk associated with the deliberate release of rAAV1-CB-hAAT in the conduct of the clinical trial is considered to be low.

An estimation of the risk to human health or the environment posed by each identified characteristic of the GMM which has the potential to cause adverse effects, is made by combining the likelihood of the adverse effect occurring and the magnitude of the consequences, if it occurs. A matrix was used by the applicant to derive the risk estimation (Table 2). Where there is scientific uncertainty, as in the case of the magnitude of the consequence of illegitimate recombination[10], the maximum magnitude is ascribed. In the case of Table 2, the magnitude of consequence of illegitimate recombination was assigned a risk of *High*.

[9] The Health and Safety Authority informed the Agency that the wild type AAV is classified as a class 1 biological agent.

[10] Illegitimate recombination is a process by which two DNA molecules with no shared homology to each other, are joined.

Table 2: Risk matrix

Characteristic of rAAV1-CB-hAAT	Magnitude of consequence	Likelihood of consequence	Risk estimation
Safety/toxicity	Moderate	Low	Low
Expression of hAAT	Low	High	Low
Immunogenicity	Low	High	Low
Homologous recombination	Negligible	Negligible	Negligible
Illegitimate recombination	High	Negligible	Negligible
Release to other humans	Low	Low	Low
Release to environment	Low	Low	Low

The risk assessment did not exclude the possibility of illegitimate recombination occurring between any sequence of the rAAV1-CB-hAAT genome and that of the human patient recipient or an unintended recipient. However, the notifier concluded in the risk assessment that the likelihood of illegitimate recombination event occurring is negligible.

Professor Gregory Atkins, a virologist from Trinity College Dublin, was retained by the Agency to provide an expert opinion on the notification. With regard to recombination, he stated the following:

> *The chances of recombination to form wild-type virus are very low and even if this did occur, the virus would not be replication competent without helper functions and would not be pathogenic.*

Duration and frequency of monitoring

The patients will be monitored for the presence of the vector DNA by the collection of blood and semen samples for 12 months after the administration of the GMM. The patient will be evaluated for the occurrence of any adverse effects at each of these visits. The patients will have 14 study visits over the course of the 12 month monitoring period. While the occurrence of adverse effects will be monitored at all of these visits, blood and semen samples will only be monitored for the presence of the GMM at 4 of the 14 study visits.

The notifier stated that in non-clinical studies in animals and previous clinical trials, vector DNA was detected at maximum concentrations in blood 1 day after administration. The vector DNA rapidly decreased over time until it was not present at all 3 months after administration. Vector DNA was not detected at all in semen samples. Based on this information the notifier is satisfied that monitoring for twelve months post administration is sufficient.

In addition to the collection of samples for detection of the vector DNA for 12 months, the patients will also continue to have annual check-ups for four years after administration of the GMM. The presence of the GMM will be

monitored indirectly during these visits through the collection of blood samples for the detection of alpha-1 antitrypsin expressed from the vector. The notifier has stated in the notification that based on the biology of the recombinant AAV vector it is expected the vector will persist in the muscle cells at sites of injection for an extended period of time, resulting in continued expression of alpha-1 antitrypsin. However, it is not expected that this would pose an environmental risk.

Professor Atkins, in his report to the Agency, stated that the level of monitoring proposed in the notification was sufficient and he did not see a necessity for the Agency to require the notifier to carry out additional monitoring for the GMM.

Condition 8.5.1 of the consent conditions, as drafted, requires the notifier to submit a report of the results of the clinical trial to the Agency. The report shall also address 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 is required to submit the report no later than the 31st December 2011. In addition to this the notifier is required, under Condition 8.5.2, to submit the results of the monitoring that will be conducted at the annual checkups for the four years after the clinical trial.

Representations made in respect of the notification

Any person may make a representation in respect of matters relating to the deliberate release of the GMM 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 Irish Times newspaper on 12th May 2010, and as such the 28 day period ended on 8th June 2010. The Agency received no representations during this period.

Waste Management

Opened vials and other contaminated solid waste will be treated by autoclaving in the Smurfit Building. The autoclave cycle will run for 15 minutes at 121˚C at a pressure of 15 p.s.i. to inactivate the GMM. The autoclave is validated on an annual basis by an external contractor. The last validation was carried out on 12th April 2010. Spore strips will be used in each run for validation. The inactivated waste will be stored for 48 hours post autoclaving to await the results of the spore tests, prior to disposal through the normal hospital waste stream.

There will be a negligible amount of liquid waste, i.e. any contaminated liquid from diluting the product during preparation for administration to the patient. This will also be treated via autoclaving under the same conditions

as above. Sharps will be stored in sharps bins and sent off site to an appropriate facility for export and incineration.

Site inspection of proposed deliberate release site

The Agency carried out a site inspection of the proposed deliberate release site, i.e., pertinent areas of Beaumont Hospital, on 25th June 2010. The Agency met with a representative from TMC Pharma Services, along with Professor Gerry McElvaney and his team who will be responsible for carrying out the clinical trial at Beaumont Hospital. The purpose of the site inspection was to verify that, if consent is granted, the proposed release will be carried out in accordance with the information supplied by the notifier and to verify that relevant information provided by the notifier in relation to the proposed site is correct. The life cycle of the GMM from its arrival at the facility, storage prior to use, use during the trial and disposal of contaminated GM material were addressed during the site inspection. Other items discussed included standard operating procedures, training of staff and emergency response plans.

Review of the notification by the EPA

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

External Review

View of the GMO Advisory Committee

The Agency consulted the GMO Advisory Committee for their views regarding the proposed clinical trial, at a meeting which was held on the 31st Mat 2010. One Committee member stated that they could foresee no difficulties given that the viral vector was replication incompetent and therefore not shed and overproduction of the antitrypsin did not appear to be problematic. The Committee raised a number of points which were clarified with the applicant through a request for further information under Article 19 of the GMO (Deliberate Release) Regulations (2003). The response to the points raised has been incorporated into this report. In general the GMO Advisory Committee did not have any major concerns with the proposed clinical trial. At the suggestion of the Agency, the GMO AC agreed that it would be a good idea to seek the expert opinion of a virologist with respect to this application since there was no expert virologist on the Committee.

Two members of the GMO AC, who were unable to attend the meeting, submitted written comments. One member commented as follows:

> *"I understand that the rAAV1-CB-hAAT virus is non-replicative and hence genetically stable and while being able to infect human cells it does not have the capacity to be toxigenic or pathogenic. The virus release will be under the strict guidance of clinical trials and hence its potential exposure to the environment is limited. There is no risk of gene flow and all waste will be appropriately destroyed and such tasks documented. As such, I believe that*

the rAAV1-CB-hAAT does not present a significant risk to the environment based on the supplied documentation."

Another member submitted the following:

"I think all precautions have been taken by the company & I don't anticipate the need for any additional specific consent conditions to be introduced by the EPA. The monitoring arrangements seem to be adequate as the patients are monitored some years after the clinical trial has been completed. My one issue might be that if in exceptional circumstances adverse effects were detected then TMC Pharma Servivces Ltd should be mandated to inform the EPA immediately so a decision on whether to stop the clinical trial immediately can be taken noting the risk to patients etc."

Agency response:
Condition 4.1 of the consent conditions as drafted, requires the consent holder to notify the Agency of any new information that could have consequences for the risks to human health or the environment as soon as any new information becomes available. This information would be evaluated by the Agency in accordance with Article 22 of the GMO (Deliberate Release) Regulations, 2003, who may, following evaluation of the information require the consent holder to modify the conditions of, suspend or terminate the deliberate release.

Benefits and concerns identified by Professor Gregory Atkins, expert reviewer retained by the EPA

Professor Atkins in his report to the Agency, in addition to points already mentioned in this inspectors report, made the following points:

The vector is an AAV with the internal rep and cap genes removed. The only regions of the AAV genome left in the vector are therefore the terminal inverted repeats. It expresses AAT from a cytomegalovirus promoter. However, the terminal repeats are from type 1 AAV and the vector particles are encapsidated in type 2 capsid protein to increase their tropism for muscle cells. The vector to be administered to patients is therefore a hybid virus. The method of preparation of the vector is not described in the application but from the above publication it appears to be the use of a cell line expressing the AAV cap and rep proteins plus functions needed from a helper virus.

There are 3 reasons why this vector could cause no adverse effect to the environment, even if shedding did occur. These are:

1) *Although administered vector is encapsidated, the vector genome does not contain either the rep or cap genes and is therefore defective. This means that the genome can only be expressed in the infected cell and can spread no further.*
2) *Even if a wild-type genome were formed, which would have to occur following recombination with endogenous AAV, the virus requires helper virus functions and cannot multiply without these.*
3) *The virus is already widespread in the population and is non-pathogenic. Similarly, the transgene is already expressed in*

most individuals and is not known to be toxic. Thus any release would have no adverse consequences.

There are no specific environmental monitoring plans described in the application. This would be possible by PCR, but would be difficult and costly. I agree with the applicants that this is unnecessary in this case. Dispersal to the environment would not occur during administration of the vector if standard laboratory practice for handling and disposal of GMMs is followed. After administration, shedding of the vector in bodily fluids may occur from the recipients but would be at high dilution and would pose no risk.

AAV vectors have been used extensively both in animal models and clinical trials (typical references given by the applicants on p2 of the Environmental Risk Assessment).

Professor Atkins stated that "*If successful this strategy would constitute a worthwhile medical advance*". As already mentioned in this report he informed the Agency that the GMO is very unlikely to cause adverse effects to the environment and as such recommended that the Agency grant consent for the trial to be conducted.

Consultation with other regulatory bodies and government departments

The Agency also consulted the following regarding the proposed deliberate release:

- Department of Health and Children
- Department of Agriculture, Fisheries & Food;
- Health & Safety Authority;
- Irish Medicines Board.

The representatives of the Department of Health and Children and the Health & Safety Authority on the Agency GMO AC submitted comments through the GMO AC meeting held on 31st May 2010. No comments were received from the Department of Agriculture, Fisheries & Food.

The IMB submitted written comments on the notification. The comments submitted by the IMB related to the clinical aspects of the trial and the recipient of the gene therapy. The comments included queries relating to the risk of carcinogenicity, justification for toxicological studies conducted by the notifier and the suitability of patients to donate tissue or cells for transplants in the future. The IMB stated in their response that these comments would most likely be more pertinent to the IMB evaluation of the trial under the clinical trial legislation previously mentioned in the introduction to this report.

The information was also sent to the Department of the Environment, Heritage and Local Government for information purposes, who requested that they be kept informed regarding the status of the notification and subsequent Agency decision.

Other EU member states

As previously stated the Agency submitted the Summary Information Notification Format 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.

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.

Condition 9.1 of the consent conditions as drafted requires the notifier to pay the Agency a once off fee of €4,788. This fee is based on the daily inspector rate. It allows for two site inspections (one during the assessment of the notification and one to be conducted if the Agency grants consent for the proposed deliberate release) and also to pay for the services of two consultants retained by the Agency during its assessment of the notification.

Recommendation

I am satisfied that on the basis of the review carried out and in particular, on the basis of the comments of Professor Gregory Atkins and the GMO Advisory Committee, that the risks posed to the environment and human health (general population) by the deliberate release of this GMM are low.

On this basis I recommend that consent be granted to Applied Genetic Technologies Corporation to conduct a clinical trial under Part B of the GMO (Deliberate Release) Regulations to test the efficacy of rAAV1-CB-hAAT in patients suffering from alpha-1 antitrypsin deficiency at Beaumont Hospital, Dublin between July 2010 and July 2011 subject to the conditions set out in the attached draft Consent Conditions.

Signed: _____ Date:_____

Suzanne Wylde
Inspector
Office of Climate Licensing & Resource Use