Consent for Notification No. B/IE/02/134.

Headquarters,
PO Box 3000,
Johnstown Castle Estate,
County Wexford, Ireland

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

GMO Register Number:	**134**
GMO notifier/user:	**Schering Health Care Ltd.,** **The Brow** **Burgess Hill** **West Sussex** **RH15 9NE** **England**
Address of Notifier:	**Schering Health Care Ltd.,** **The Brow** **Burgess Hill** **West Sussex** **RH15 9NE** **England**

Genetically Modified Organisms Regulations, 1994 (S.I. No. 345 of 1994)

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

Decision of the EPA, under Article 33 (3) (a) of the Genetically Modified Organisms Regulations, 1994 (S.I. No. 345 of 1994).

Reference No: B/IE/02/134

Register of Genetically Modified Organisms (GMOs) Users in Ireland: No. 134

The EPA in exercise of the powers conferred on it by the Genetically Modified Organisms Regulations, 1994 (S.I. No. 345 of 1994) hereby grants consent to:

Schering Health Care Ltd
The Brow
Burgess Hill
West Sussex
RH15 9NE
England

to carry out the following activity:

A deliberate release into the environment of a GMM, a Gene Therapy Product, AdFGF-4, for purposes other than for placing on the market in the following four locations;

1. University College Hospital, Galway
2. St James's Hospital, James's Street, Dublin
3. Mater Misericordiae Hospital, Eccles Street, Dublin
4. Beaumont Hospital, Beaumont Road, Dublin

The period of release extends from September 2002 to February 2006.

SEALED by the Seal of the Agency on this day, 20th September 2002

PRESENT when the seal of the Agency was affixed hereto:

Director/Authorised Person

DECISION

The EPA, in exercise of the powers conferred on it by the Genetically Modified Organisms Regulations 1994, S.I. No 345 of 1994 for the reasons hereinafter set out, grants this consent to:

Schering Health Care Ltd., The Brow, Burgess Hill, West Sussex, RH15 9NE, England.

to carry on the deliberate release into the environment for purposes other than for placing on the market in four locations;

University College Hospital, Galway
St James's Hospital, James's Street, Dublin
Mater Misericordiae Hospital, Eccles Street, Dublin
Beaumont Hospital, Beaumont Road, Dublin

subject to eleven 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:

- the patient receiving the treatment insofar as they are part of the general population and the wider environment;
- the potential risk of the GMM moving from the patient to the general population and the consequences of such a risk; and,
- 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, supporting and opposing documentation received in respect of the notification, and the report of its inspector.

The consent is granted in accordance with Article 33 (3) (a) of the Genetically Modified Organisms Regulations 1994, S.I. No. 345 of 1994.

CONSENT FOR

The deliberate release into the environment of a GMM for purposes other than for placing on the market.

Consent Conditions for GMO Register Entry No. 134

1. **Scope**

(a) This consent is for the purposes of compliance with the Genetically Modified Organisms Regulations, 1994 (S. I. No. 345 of 1994) only, in relation to the carrying out of deliberate release trials (clinical trials) as specified in Condition 2.

(b) Nothing in this consent shall be construed as negating the licensees statutory obligations or requirements under any other enactments or regulations. A further consent is required from the Irish Medicines Board (IMB) under the Control of Clinical Trials Act 1987 and the Control of Clinical Trials and Drugs Amendment Act 1990. The notifier must fulfil other legislative obliglations , for example, any obliglations, under the relevant Safety Health and Welfare at Work Acts and relevant Hospital Health and Safety regulations, as applicable.

Reason: To clarify the scope of the consent

2. **Location of the Trials**

This consent covers the treatment of clinical trial patients at four (4) sites at the following hospitals, from September 2002 to February 2006.

(a) University College Hospital, Galway
(b) St James's Hospital, James's Street, Dublin
(c) Mater Misericordiae Hospital, Eccles Street, Dublin
(d) Beaumont Hospital, Beaumont Road, Dublin

Reason: To clarify the area and the locations of the trials

3. **Containment Measures to be Used at the Deliberate Release Sites**

The following containment measures shall apply at each site.

(a) The general principles of good microbiological practice and of good occupational safety and hygiene as outlined in Part A of the Fourth Schedule of S. I No 73 of 2001 (reproduced in Annex 1 attached). Items iv and vi in the Annex are not relevant to this consent.

(b) Level 2 containment measures as outlined in the notification and as set out in Tables IA of the Fourth Schedule of S. I. No. 73 of 2001 (reproduced in Annex II attached), including measures 7, 13 and 14.

(c) Following injection of the GMM, each patient shall be hospitalised overnight in a single-bedded room for a minimum of 24 hours, or longer, if required by the hospital medical staff.

(d) Prior to the date of commencement of the deliberate release, the notifier shall implement, or plan for the implementation of, the following SOPs.

- Receipt of the GMM (the study product) from the Notifier.
- Secure storage of the GMM.
- Preparation of the GMM (study product).
- Cardiac catherterisation laboratory procedure/administration of the GMM.
- Patient management for 24 hour post-injection period.
- 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.
- Transport, movement and handling of GMMs within the trial site and outside the trial site, where relevant.
- Emergency planning, as outlined in the notification.
- Training of staff.

Copies of these SOPs shall be sent to the EPA, for approval[1], and to the relevant hospital staff[2], two (2) weeks in advance of the initial deliberate release.

(e) Designated persons responsible for the implementation of the SOPs mentioned in 3(d) above shall be identified by the notifier, for each site, and their names forwarded to the EPA and the relevant hospital staff two (2) weeks in advance of the initial deliberate release. Any changes to these designations that occur during the course of the trial at any site shall be notified immediately to both the EPA and the relevant hospital staff.

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

[1] Prior to commencement of the trial EPA approval will be required for the elements of these SOPs relating to the management of the GMM.

[2] '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.

4. **Worker Protection Measures To Be Taken During the Release**

(a) Worker protection measures to be taken during the release, as outlined in the notification, shall be implemented during the release and shall be made available to and used by the staff involved in the execution of the trial. An SOP setting out these worker protection measures and how they will be implemented shall be sent to the EPA, for approval[3], and to the relevant hospital staff two (2) weeks before the initial release takes place.

(b) Designated persons responsible for the implementation of the SOPs mentioned in 4 (a) above shall be identified by the notifier, for each site, and their names forwarded to the EPA and the relevant hospital staff two (2) weeks in advance of the initial deliberate release. Any changes to these designations that occur during the course of the trial at any site shall be notified immediately to both the EPA and the relevant hospital staff.

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

5. **Record Keeping**

(a) A copy of the training record regarding worker protection measures, as set out in the notification, shall be signed by all relevant staff and approved by the Principal Investigators. Copies shall be sent to the Health and Safety Co-ordinator at the hospital, the Chief Executive Officer at the hospital and the EPA prior to the commencement of each release.

Reason: To ensure that all relevant staff are adequately trained before the deliberate release of the GMM commences.

6. **Management of un-used GMM Material and GMM Wastes**

(a) All un-used GMM material and GMM waste shall be disposed of in accordance with information supplied in the notification. An SOP setting out measures to be used to manage un-used GMM material and GMM waste and how these measures will be implemented shall be provided to the EPA, for approval, and to the relevant hospital staff two (2) weeks before the initial release takes place.

[3] Prior to commencement of the trial EPA approval will be required for the elements of these SOPs relating to the management of the GMM

(b) A designated person responsible for the implementation of the SOP mentioned in 6(a) above shall be identified by the notifier, for each site, and the person's name forwarded to the EPA and the relevant hospital staff two (2) weeks in advance of the initial deliberate release. Any changes to this designation that occur during the course of the trial shall be notified immediately to both the EPA and the relevant hospital staff.

(c) Records of all GMM inactivation events, e.g., autoclave printouts, (of both unused GMM material and GMM waste) shall be maintained, signed off by the relevant Principal Investigator and made available for inspection by the EPA.

(d) Any spillages, accidents or other unforeseen incidents involving GMM material shall be notified immediately to the EPA and the relevant hospital staff. The notifier shall submit a report to both the EPA 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.

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.

7. **Duty of the Notifier to Inform the EPA of New Information**

(a) If, following the grant of written consent by the EPA to the deliberate release, there is a modification of the deliberate release which could have consequences for the risks to human health or the environment, or if new information on such risks becomes available, the company must:

- ⇒ revise the measures specified in the notification,
- ⇒ inform the EPA in advance of any modification or as soon as the new information is available, and
- ⇒ take all measures necessary to protect human health and the environment.

(b) The EPA may, having examined any modification or new information for compliance with the Regulations and evaluated the risks, require the notifier to modify the conditions of, suspend or terminate the deliberate release.

Reason: To provide and update information on the trial.

8. **Monitoring**

(a) The viral shedding monitoring programme as outlined in the notification shall be carried out. An SOP setting out the details of this monitoring programme and how it will be implemented shall be submitted to the EPA, for approval, and to the relevant hospital staff, two (2) weeks prior to the initial release. This SOP should include details of how the monitoring techniques proposed were validated for this GMM.

(b) Designated persons responsible for the implementation of the SOPs mentioned in 8 (a) above shall be identified by the notifier, for each site, and their names forwarded to the EPA and the relevant hospital staff two (2) weeks in advance of the initial deliberate release. Any changes to these designations that occur during the course of the trial at any site shall be notified immediately to both the EPA and the relevant hospital staff.

Reason: To ensure compliance with the conditions of this consent.

9. **Reporting to the EPA**

(a) The notifier shall inform the EPA, in writing, two weeks in advance of any patient administration of the GMM, of the names of each patient and the date on which the patient will be administered the GMM.

(b) Results of viral shedding monitoring for each patient, who is administered with the GMM, shall be sent to the EPA as soon as they become available. In addition, an annual report on the viral shedding monitoring activities described in the notification, trial results and the conclusions arrived at by the notifier, shall be submitted by the notifier to the EPA by December 31st, 2002, 2003, 2004, 2005 and 2006.

(c) After completion of the trials, the notifier shall send to the EPA the results of the deliberate releases and, in particular, shall submit an assessment of any risks to human health or the environment resulting from the deliberate releases, with particular reference to any product that the notifier intends to notify at a later stage which may contain the GMM which was deliberately released.

Reason: To provide for the collection and reporting of adequate information on the trial during the course of the trial and to make provision for the reporting to the EPA of any impacts of the completed trials and any associated risks.

10. **Molecular & Laboratory Work Connected With Monitoring**

If the EPA decides to carry out laboratory analysis using PCR or other methods in relation to this trial, these costs will be charged to the notifier.

Reason: To ensure that the EPA can identify the GMM.

11. **Charges for carrying out site inspections, auditing monitoring results**

The company shall pay the EPA a contribution of €13,320.00

Reason: To provide for adequate financing for site inspections and auditing the monitoring results and financial provision 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 IA

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

Measures		Containment levels			
		1	2	3	4
1	Laboratory suite: isolation	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	Required
19	Observation window or alternative to enable occupants to be seen	Optional	Optional	Optional	Required

For the purposes 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 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 a 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.