This Memo has been cleared by the Programme Manager OCLR for submission to the Board
Signed: Bea Claydon Dated: 20 Sept 11

Environmental Protection Agency
An Ghníomhaireacht um Chaomhnú Comhshaoil

OFFICE OF CLIMATE,LICENSING & RESOURCE USE

INSPECTOR'S REPORT

TO:	**BOARD OF DIRECTORS**
FROM:	Suzanne Wylde - **Environmental Licensing Programme**
DATE:	20th September 2011
RE:	Notification from Professor Samuel McConkey, Royal College of Surgeons in Ireland, under Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) to conduct a clinical trial using two genetically modified micro-organisms (GMMs) (GMO Register No: G0451-01).

Applicant:	Professor Samuel McConkey, Department of Tropical Medicine and International Health, Royal College of Surgeons in Ireland, 123 St Stephens Green, Dublin 2.
GMO Register Entry No:	G0451-01
SNIF No:	B/IE/11/451(a) & B/IE/11/451(b)
Notification under Article 14(1) of S.I. No 500 of 2003:	The deliberate release of a genetically modified organism for purposes other than placing on the market (Part B Release – Clinical Trial).
Timeframe for EPA's Decision under Article 18(5) of S.I. No 500 of 2003:	A person shall not deliberately release a genetically modified organism (GMO) for purposes other than placing on the market unless consent in writing has been granted by the EPA. The EPA shall communicate its decision (either grant consent with or without conditions or refuse consent) in writing to the notifier within **90 days** of receipt of the notification.
Date of receipt of notification under Article 14 of S.I. No 500 of 2003:	12th July 2011
Request for additional information under Article 19 of S.I. 500 of 2003:	30th August 2011
Additional Information submitted under Article 19 of S.I. 500 of 2003:	14th September 2011
Date by which decision is required:	24th October 2011
Representations to the EPA relating to this notification under Article 16 of S.I. 500 of 2003:	None to date

Introduction

Professor Samuel McConkey of the Department of Tropical Medicine and International Health, Royal College of Surgeons in Ireland notified the Environmental Protection Agency (Agency) on 12th July 2011 of an intention to conduct a clinical trial on patients to assess the safety and immunogenicity of a new malaria vaccine, using two genetically modified micro-organisms (GMMs). The notifier proposes 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 2nd August 2011.

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 (G0134-01) in 2002 and Applied Genetic Technologies Corporation (G0362-01) in 2010, to conduct clinical trials.

The GMMs for the proposed clinical trial are a replication deficient[3] chimpanzee adenovirus and a replication deficient modified vaccinia virus Ankara. Both of these viruses have been engineered to express the malaria circumsporozoite protein. The GMMs are described in further detail later in this report under "*Description of the Genetically Modified Micro-Organism for use in the proposed clinical trial*".

Malaria is caused by a parasite called Plasmodium, which is transmitted via the bites of infected mosquitoes. In the human body, the parasites multiply in the liver, and then infect red blood cells.

The World Health Organisation estimates that each year 300-500 million cases of malaria occur and more than 1 million people die of malaria, particularly in developing countries. Most deaths occur in young children. It should be noted that many countries with malaria are already among the poorer nations. The disease maintains a vicious cycle of disease and poverty.

Although recent evidence suggests that the epidemiology of malaria is changing across certain parts of Africa, the worldwide burden of malaria remains a major public health problem. The development of resistance both in mosquitoes to certain insecticides and of malaria parasites to chemotherapeutic agents has contributed to an increasing need for a new, effective prevention or treatment of malaria. Thus, the need to carry out clinical trials such as the one described in this report.

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[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] Replication deficient means the viruses have been engineered so that they cannot replicate in human cells.

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.

The use of viruses in combating human diseases

In recent times it has become apparent that some characteristics of viruses[4], 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 viruses and RNA viruses that synthesise a DNA copy of their genome such as retroviruses.

In this proposed clinical trial, disabled chimpanzee adenovirus and Modified Vaccinia virus Ankara (MVA) vectors will be used to 'piggy back' a protein into patients to vaccinate against malaria.

MVA was originally derived from the vaccinia strain Ankara by over 500 serial passages in avian cells. It was used, successfully, in the worldwide eradication of smallpox.

Adenoviruses in humans rarely cause serious illness, although they commonly cause self-limiting respiratory tract, ocular and gastrointestinal infections. However, the adenovirus proposed for use in this trial is a chimpanzee adenovirus

[4] 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

and is not capable of replication in human tissue. Chimpanzee adenoviruses have been developed as viral vectors following concerns that pre-existing human immunity to human adenoviral serotypes could limit future widespread use of these viruses.

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

(i) Chimpanzee Adenovirus 63 CS (ChAd63 CS)
This is a replication deficient chimpanzee adenovirus, which has been engineered to express the malaria circumsporozoite protein (CS).

(ii) Modified Vaccinia virus Ankara CS (MVA CS)
This is a replication deficient virus related to the virus used in the successful smallpox vaccination campaign. Unattenuated vaccina virus (meaning the virus has not been engineered to have reduced virulence) has been engineered to express the malaria circumsporozoite protein.

Purpose of the proposed deliberate release

The primary objective of the trial is to assess the safety of new candidate malaria vaccines ChAd63 CS administered alone and with MVA CS in a prime-boost regime to healthy volunteers.

The secondary objective of the trial is to assess the humoral[5] and cellular immune responses generated by ChAd63 CS when administered to healthy volunteers alone and with MVA CS.

Proposed location of the deliberate releases

The proposed location for the deliberate release is the Clinical Research Centre, Beaumont Hospital, Beaumont Road, Dublin. It is envisaged that there will be twenty four patients treated at Beaumont Hospital.

Timeframe for the proposed clinical trial

The notification requested the treatment of clinical trial patients at the named hospital location from 1st September 2011 to 31st December 2012. As the 1st September has passed, (it is within the 90 day assessment period), the date of commencement of the trial will be the date of grant of consent conditions by the Agency in relation to the trial.

Method(s) & quantities to be used for the release

The GMM will be administered to the patient as an intramuscular injection. There will be a total of 24 patients involved in the trial, divided into two groups (Table 1). Group 1 will consist of two sub groups. Subgroup A will receive one dose of the ChAd63 CS, while subgroup B will receive one dose of ChAd63 CS followed 8 weeks later by one dose of the MVA CS. Group 2 will be treated in the same divisions as Group 1 but with higher dosages. There will be a minimum interval of

[5] The humoral immune response is one of two main arms of the immune system. This response sees the immune system trigger specific B cells to proliferate and secrete large amounts of their antibodies. These antibodies can then combat a particular microorganism or virus and thereby prevent infection.

two weeks between administration of ChAd63 CS to the last volunteer in Group 1 and the first volunteer in Group 2.

Table 1: Overview of trial groups and dosages.
(vp = virus particles; pfu = plaque forming unit)

Group number	No. of volunteers	ChAd63 CS Day 0	MVA CS Day 56
1A	4	5×10^9 vp	-
1B	8	5×10^9 vp	2×10^8 pfu
2A	4	5×10^{10} vp	-
2B	8	5×10^{10} vp	2×10^8 pfu

The first 3 volunteers to receive each vaccine, at each dose, will be asked to remain in Beaumont Hospital for a period of 12 hours post vaccination to monitor for any possible adverse effects the vaccinations may have. They will then be asked to return for a clinical review the following day. Other than these first three volunteers, volunteers will not be asked to remain in the hospital for any length of time.

In order to minimise dissemination of the recombinant vectored vaccine virus into the environment, the inoculation site will be covered with a dressing after immunisation. This should absorb any virus that may leak out through the needle track. The dressing will be removed from the injection site after 30 minutes (+/- 5 minutes) and will be disposed as GM waste by autoclaving.

Storage & Preparation of the GMM prior to release/administration

CHAd63 CS will be formulated and vialed at the Clinical Biomanufacturing Unit (CBF), University of Oxford. The MVA CS will be formulated and vialed at a company in Germany. It will then be shipped to the CBF at Oxford, where all vials will be labelled '*for investigational purposes only*'. The vials will then be shipped on dry ice from the CBF to the RCSI.

The ChAd63 CS is supplied as a liquid in sterile clear glass 2ml aliquots. The MVA CS is supplied in a virus suspension in sterile clear glass 2ml aliquots. For the ChAd63 CS vaccine the notifier expects to receive delivery of 26 vials, to include two spare vials. The notifier expects to receive 36 vials of the MVA vaccine, to include 4 spare vials. The vials will be stored for the duration of the study, 6 to 12 months. Any remaining vials will be shipped back to the University in Oxford for storage or destruction via permission from both the project sponsor and the appropriate authority in the UK.

Vials of ChAd63 CS and MVA CS will be stored in a dedicated section of a locked freezer between -70°C and -90°C. The freezer is located in a key code protected room, in an area of the building which has restricted access (swipe card). All movements of the study vaccines will be documented. Vaccine accountability, storage, shipment and handling will be in accordance with local SOPs.

On vaccination day the vaccines will be allowed to thaw to room temperature and administered within 1 hour of reaching the desired temperature.

Worker protection measures taken during the release

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.

Information about previous releases with these GMMs

While neither MVA CS nor ChAd63 CS have been administered to humans before, the route and dose of the vaccines is based on experience using the same vectors (i.e. MVA and ChAd63, without the circumsporozoite (CS)) in Phase 1 and Phase 2 clinical trials in the UK and Africa.

ChAd63 has been administered to more than 250 healthy individuals and the vector has been repeatedly shown to be safe at the proposed dosages above.

MVA has been administered to more than 120 healthy adults following priming with ChAd63 expressing the same antigen, at various doses.

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 two GMMs in question in this trial are replication incompetent, i.e. the GMMs cannot replicate in human cells. The AdCh63 CS is a modified adenovirus recombinant virus vaccine. AdCh63 CS is rendered replication deficient by deletion of the E1 region which contains genes essential for the initiation of viral replication. MVA CS is a modified recombinant virus vaccine derived from the attenuated virus, Modified Vaccinia Ankara. Modified vaccinia virus Ankara (MVA) is a highly attenuated vector that is unable to replicate efficiently in human and most other mammalian cells.

If either MVA CS or ChAd63 CS re-acquired the ability to replicate reliably, the consequences would likely be minimal, with local antibody responses likely adequate to suppress any infection. In the case of MVA CS this follows on from

the use of the un-attenuated vaccinia virus being used safely in the campaign to eradicate smallpox from humans.

Malaria sporozoites[6] make a remarkable journey from the mosquito midgut to the mammalian liver. The sporozoite's major surface protein, circumsporozoite protein (CS), is a multifunctional protein required for sporozoite development and likely mediates several steps of this journey. The genetic modification of the two vectors involved in this trial, is to express the circumsporozoite protein. This genetic modification is unlikely to lead to any deleterious effects in the event of this gene being transferred to other viruses.

The circumsporozoite protein itself does not have pathogenic effects in humans. PCR analysis has been used to demonstrate the presence of the CS antigen[7] coding sequence and absence of any parental virus. Also the antigen in the virus has been sequenced and was not found to have undergone any mutations or deletions.

These are non-replicating, non-integrating viral vectors. They are not expected to be able to persist in the body or in the environment. This means that the vector will only be transiently present in the human body. The mechanism of action of both vectors is the expression of the malaria antigen CS encoded by the viral vectors and stimulation of a cellular immune response to the expressed protein.

Given the inability of both GMMs to replicate, it is unlikely that a release to the wider environment could occur. Theoretically, there could be minor leakage of the vaccines from the inoculation site. This could be a mode of contaminating the local environment. However, this risk will be reduced by covering the inoculation site with a dressing after vaccination and appropriately disposing the dressing, as discussed earlier.

The ChAd63 CS and MVA CS vaccinations are currently being tested in mice. The study is ongoing and the animals have all been reported healthy after receiving both vaccines. Control animals were being administered PBS[8] at the same time. It is not expected that there will be any difference between PBS-injected mice and the vaccine injected mice, other than those attributable to the administration of the vaccine.

A previous study was also conducted on mice using similar malaria vaccines (MVA and ChAd63 based). The aim of the study was to investigate the potential toxicity of the malaria vaccines in mice when administered intra-muscularly. There were no deaths or adverse effects of treatment except for those attributable to the administration of a vaccine manifested as inflammatory and immune responses at the injection site. The treatment was not associated with any systemic toxicological changes.

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[6] A sporozoite is the cell form that infects new hosts. In malaria, for instance, the sporozoites are cells that develop in the mosquito's salivary glands, leave the mosquito during a blood meal, and enter the liver where they multiply. Cells infected with sporozoites eventually burst, releasing more spores into the bloodstream.

[7] An antigen is a substance or molecule that, when introduced into the body, triggers the production of an antibody by the immune system, which will then kill or neutralize the antigen that is recognized as a foreign and potentially harmful invader.

[8] Phosphate buffered saline (PBS) is a buffer solution commonly used in biological research. It is a water-based salt solution. The buffer helps to maintain a constant pH. The osmolarity and ion concentrations of the solution usually match those of the human body (isotonic).

MVA CS has been shown to be immunogenic in mice. Distribution studies in mice showed no evidence of replication of the virus or presence of disseminated infection 1 week after intradermal and intramuscular injections using similar MVA vaccines. Toxicology studies showed no evidence of systemic MVA related toxicity after administration.

The notifier concluded in the risk assessments that given the proven history of both MVA and adenoviral vaccines and the benign nature of the protein product of the inserted gene, the overall risk associated with the GMMs is low.

Duration and frequency of monitoring

Clinical reviews will be carried out on all volunteers 90 days prior to administration of the vaccine. The notifier provided a detailed schedule of clinical reviews for all of the study groups in the notification. Where the ChAd63 CS vaccine is being administered alone clinical reviews will be carried out at days 0, 1, 14, 28, 56 and 90. Day 0 being the day of administration of the vaccine. Where both vaccines are to be administered, clinical reviews will be carried out on days 0, 1, 14, 28, 56, 57, 63, 84 and 140. Day 0 being the administration of ChAd63 and day 56 being administration of MVA CS.

The clinical reviews post administration consist of medical history, physical examination, local and systemic adverse events assessed and blood work. The blood work is not carried out on day 1 and, in the case of MVA CS, on day 57.

The clinical trial does not propose to attempt to detect MVA or ChAd63 in the patients after vaccinations. In earlier clinical studies of MVA vectored vaccines, the research group attempted to detect MVA at the vaccine site and were unable to detect any vaccine present. The research group stated that both themselves and the ethical committees, regulatory authorities (UK based) '*have not seen the value in repeating consistently negative shedding studies with MVA and non-replication competent viral vectors to repeatedly prove the absence of shedding with these very well studied viral vectors*'. This view was reflected in the response of the virologist on the GMO Advisory Committee, discussed later in this report.

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 1st June 2013, six months after end of the 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 Evening

Herald newspaper on 14th July 2011, and as such the 28 day period ended on 11th August 2011. The Agency received no representations during this period.

Waste Management

All material (sharps, dressings, gloves, empty vials, etc) used in the vaccination process is placed in an open sharps container. The material is autoclaved and then placed in biohazard bags for incineration off-site. The autoclave inactivation cycle will be run at 125°C for 15 minutes at a pressure of 1.4 bar.

The autoclave is located on the ground floor of the laboratory department of Beaumont Hospital, directly accessed via secure swipe card access from the Clinical Research Centre. The autoclave is validated annually. The last validation took place on 28th March 2011.

The clinicians or nurses administering the vaccines will be responsible for autoclaving the waste post vaccination. They will also be responsible for completing a laboratory log and clinical trial log recording the waste inactivation and its fate post autoclaving.

Site inspection of proposed deliberate release site

There are a number of registered contained use users at the Smurfit Building, Beaumont Hospital. The premises have been inspected on a regular basis by the Agency in line with its policy of inspecting contained use facilities once every three years.

The premises were also inspected in June 2010 as it was the proposed site for another clinical trial using GMMs[9]. The Agency is satisfied that, if the clinical trial were to go ahead at this premises, it would be conducted in compliance with the legislation.

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 27th July 2011.

In general the GMO Advisory Committee did not have any major concerns with the proposed clinical trial and were in support of the trial going ahead. The Agency received written comments from four members of the GMO Advisory

[9] This trial did not go ahead in Ireland for logistical reasons.

Committee, one of whom is a virologist. One Committee member requested that the Agency seek the advice of a virologist.

The virologist stated that both vectors proposed are well known vectors. In the case of the ChAd63 CS there is a small possibility of recombination with human adenovirus but in his opinion this possibility is negligible. The MVA virus has been passaged many times in avian cells and has lost its ability to multiply in human cells. The circumsporozoite protein to be expressed has been used in clinical trials previously. It is well tolerated and is unlikely to cause harm to humans or the environment. The virologist concluded to say that the GMMs do not pose a significant risk to the environment.

Two members of the committee requested that the notifier should submit further information on the precautions that will be taken against accidental release such as spillage and the containment conditions to be used.

Agency response:
The Agency requested that the aforementioned information be submitted as part of the assessment process and it has been incorporated into this report. The GMMs are classified as Class 1 GMMs, those having low or negligible risk. Condition 5.1 of the consent conditions addresses the containment measures to be put in place at the deliberate release site.

Another Committee member stated that as this trial is to be conducted in the UK also, the EPA should co-operate with the UK authorities on this issue to ensure that in both cases all the correct conditions are being followed in both jurisdictions.

Agency response:
The authorities in the UK assess clinical trials under the contained use legislation. As such, the conditions that will be put in place in both jurisdictions will differ considerably.

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;
- Irish Medicines Board (IMB).

The representatives of the Department of Health and Children and the Health & Safety Authority on the Agency GMO AC did not have any comments to make. No comments have been received from the Department of Agriculture, Fisheries & Food.

The IMB responded stating that it considered the overall environmental impact for both vectors to be low and that appropriate measures are being taken to avoid any potential adverse effects on humans and/or the environment. In relation to the notification to the IMB in accordance with the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations, the 60 Day timeframe

ends on 3rd October 2011. The IMB expects to grant conditional approval sometime after 3rd October 2011, as they are awaiting further information relating to batch analysis of the ChAd63 CS vector.

The information was also sent to the Department of the Environment, Heritage and Local Government for information purposes.

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.

Recommendation

I am satisfied that on the basis of the review carried out and in particular, on the basis of the comments of 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 Professor Samuel McConkey at RCSI to conduct a clinical trial under Part B of the GMO (Deliberate Release) Regulations to test the safety and immunogenicity of a malaria vaccine at Beaumont Hospital, Dublin from the date of grant of consent conditions by the Agency to 31st December 2012 subject to the conditions set out in the attached draft Consent Conditions.

Signed: _____ Date: 20/9/2011

Suzanne Wylde
Inspector
Office of Climate Licensing & Resource Use