OFFICE OF CLIMATE,LICENSING & RESOURCE USE

INSPECTOR'S REPORT

TO:	BOARD OF DIRECTORS
FROM:	Bernie Murray - Environmental Licensing Programme
DATE:	26 June 2014
RE:	Notification from the GUIDE Department (Department of Genito Urinary Medicine and Infectious Diseases), St James's Hospital, Dublin 8 under Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003) to conduct a clinical trial using a GMO (GMO Register No: G0536-01).

Applicant:	The GUIDE Department (Department of Genito Urinary Medicine and Infectious Diseases), St James's Hospital, Dublin 8
GMO Register Entry No:	G0536-01
SNIF No[1]:	B/IE/14/01 & B/IE/14/02
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:	14 April 2014
Request for additional information under Article 19 of S.I. 500 of 2003:	13 May 2014
Additional Information submitted under Article 19 of S.I. 500 of 2003:	23 May 2013
Date by which decision is required:	22 July 2014

[1] Summary of the notification forwarded to the European Commission for circulation to all member states

Representations to the EPA relating to this notification under Article 16 of S.I. 500 of 2003:	0

Introduction

The GUIDE Department (Department of Genito Urinary Medicine and Infectious Diseases), St James's Hospital, Dublin 8, sought the consent of the Environmental Protection Agency (Agency) on 14 April 2014 to perform a Phase 1 clinical trial on an immunisation strategy with novel candidate Hepatitis C vaccines comprising Genetically Modified Organisms (GMOs).

The notifier proposes to conduct this trial at the Wellcome Trust-HRB Clinical Research Facility, St James's Hospital, Dublin 8. The notification was made in accordance with Part II of the GMO (Deliberate Release) Regulations (S.I. 500 of 2003).

It is estimated that 3% of the world's population is infected with Hepatitis C virus (HCV). In Ireland it is estimated that 20,000 – 50,000 people are chronically infected with HCV, a population prevalence of 0.5 – 1.2%, which is similar to other countries in Northern Europe.

HCV is primarily contracted through intravenous drug use. Less frequent methods of transmission include perinatal exposure, hemodialysis, and sexual contact with an HCV infected person.

Once infected, some people live with the virus without any problems but in others the virus over many years causes liver scarring, eventually liver cirrhosis, liver cancer and liver failure (chronic infection). There is no vaccine for Hepatitis C however efforts are being made to develop one.

The GMOs proposed to be released are viral vectors (Chimpanzee Adenovirus 3 and Modified Vaccinia Virus) containing the NSmut gene encoding a non-structural region of HCV genotype 1b - the commonest subtype of Hepatitis C in Europe. The GMOs are abbreviated to AdCh3NSmut1 and MVA-NSmut.

The objective of this proposed clinical trial is to assess Hepatitis C vaccines for safety and immunogenicity in HIV-1 seropositive individuals who are on anti-retroviral therapy and Hepatitis C unaffected. HIV-1 seropositive / Hepatitis C unaffected individuals are selected owing to increased risk of Hepatitis C virus infection due to the similar routes of acquisition of both viruses. There is an urgent need for preventive measures including the development of HCV vaccines.

Applications in respect of four clinical Part B trials have been assessed and approved by the Agency since 2002. G0451 under Prof Samuel McConkey, RCSI, was approved by the Agency in 2011 and entailed the use of the same viral vectors (Chimpanzee Adenovirus and Modified Vaccinia Virus) as will be used during this proposed trial. G0451 was completed in 2012 and the viral vectors were demonstrated to be both safe and immunogenic.

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 to human health or the environment.

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

This notification entails two GMMs:

1. AdCh3NSmut1 – a modified recombinant virus derived from an attenuated replication-incompetent chimpanzee adenovirus;
2. MVA-NSmut - a recombinant virus vaccine derived from the attenuated virus, Modified Vaccinia Ankara.

Both vectors are genetically modified to promote the expression of Hepatitis C immunogen NSmut.

Each vector constitutes a separate vaccine. The vaccines will be administered 8 days apart.

Purpose of the proposed deliberate release

The purpose of the trial is to perform a Phase 1 clinical trial on an immunisation strategy with novel candidate Hepatitis C vaccines in Human Immunodeficiency Virus-1 (HIV-1) seropositive individuals who are Hepatitis C unaffected. The vaccines will be assessed for safety and immunogenicity.

Proposed location of the deliberate releases

The proposed deliberate release will be performed at the Wellcome Trust / Health Research Board (HRB) Clinical Research Facility (CRF), St James's Hospital, James's Street, Dublin 8.

Timeframe for the proposed clinical trial

This proposed trial will take place during the period July 2014 – December 2015 however prior IMB approval will also be required.

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, S.I. No 500 of 2003.

AdCh3NSmut1

Wild type Adenovirus is classified as a Group 2 biological agent under the Biological agents at work Directive 93/88/EEC. Unmodified Adenovirus is of limited pathogenicity. It can produce respiratory tract infections, gastro intestinal disturbances and ocular infections. Most members of the population are seropositive and can produce neutralising antibodies against adenoviruses.

The GMM AdCh3NSmut1 is derived from AdCh3, a recombinant attenuated chimpanzee adenovirus. Simian adenoviruses are not known to cause pathological illness in humans and while the prevalence of antibodies to chimpanzee adenovirus in humans is unknown in Ireland, data from other developed countries typically cites a seroprevalence rate of less than 5%. Furthermore, this adenoviral strain is rendered replication incompetent by deletion of the E1 region. Normally the E1 region contains genes essential for the initiation of viral replication. Replication deficient adenoviruses lacking the E1 region are classified as Biosafety Level 1.

MVA-NSmut

The GMM MVA-NSmut is derived from Modified Vaccinia Virus Ankara (MVA) which is a highly attenuated strain of vaccinia virus. MVA was originally developed as a vaccine against smallpox and has a history of safe use. MVA vaccines are not in routine use in Ireland at present. Therefore, the seroprevalence of antibodies to MVA is expected to be extremely low.

MVA has lost approximately 15% of the original vaccinia genome which has significantly reduced its virulence and pathogenesis in both healthy and immuo-compromised humans and animals. It is unable to replicate efficiently in human and in most mammalian cells. In addition, the MVA genome cannot integrate into the genome in the nucleus of the infected cell. Rather, it remains localised in the cell's cytoplasm.

The Insert

The insert is NSmut, a 1,985 amino acid sequence encompassing NS3 to NS5B of the non-structural region (NS) of HCV. NSmut has a genetically inactivated NS5B polymerase the purpose of which is to limit any potential replication capacity for the vaccine.

NSmut is inserted into the AdCh3 backbone in place of the E1 region.

The purpose of NSmut is to induce T-cell immune responses against Hepatitis C virus with a view to conferring protection against Hepatitis C chronic infection.

Risks to Human Health

Both the AdCh3 and the MVA viral vectors are non-replicating, non-integrating viral vectors. This means that the vectors will only be transiently present in the human body. They are not expected to be able to persist in the body or in the environment.

In the event of the vaccine coming into contact with the cornea there is a theoretical risk of cellular infection and ulceration. However a mitigating measure will be the use of eye protection and the use of SOPs for drawing up and administering the vaccine as well as safe disposal of waste.

Immune response

The mechanism of action of both vectors is the expression of the HCV immunogen NSmut which in turn will induce T cell immune responses to Hepatitis C antigens which may confer protection against chronic infection.

Shedding

A Phase I clinical trial carried out in Oxford from July 2007 to February 2011 assessed the safety and immunogenicity of AdCh3NSmut in healthy volunteers during which no Adenoviral vector was detected in urine samples or throat swabs. These findings were consistent with preclinical studies demonstrating no vector dissemination beyond regional lymph nodes and no vector persistence.

MVA is incapable of replication in human cells. Therefore after the initial infection of the cells that the virus enters there will be no further infection and no spread of the virus within the body.

Theoretically there could be minor leakage of the vaccine from the inoculation site. The dose would be small compared to the inoculation dose and the risk of transmission to other individuals extremely low. This risk will be mitigated by covering the inoculation site with a dressing which will be removed after 30 minutes and disposed of as GMO waste.

Germline transmission

There is no potential for germline transmission since there is no viral vector shedding in the semen.

Homologous Recombination

Human Adenoviral infection in humans is transient. Furthermore given that viral vector AdCh3 is replication defective and does not disseminate or persist in the host, the theoretical risk of recombination of the vector with human adenoviruses *in vivo* is very low.

As already mentioned, MVA corresponds to a highly attenuated strain that has lost approximately 15% of the initial vaccinia genome. Although the risk of reconversion to wild type can be considered as negligible it has been suggested that some of the disrupted or deleted genes could be rescued by recombination in case of co-infection of a MVA based vaccine and a naturally occurring orthopoxvirus. Such an event however is considered as extremely rare. According to the notifier recombinant MVA vaccines have been safely administered to HIV-infected individuals in several clinical trials.

Risks to the Environment

Given the inability of the viral vectors (AdCh3 and MVA) to replicate in mammalian cells it is unlikely a significant release to the wider environment could happen.
MVA vaccines have been used extensively in the past with no environmental concerns and are generally well tolerated with few safety concerns to human health.

Storage, preparation and administration of the vector

Receipt and storage of vaccine will be the responsibility of the pharmacy in the Clinical Research Facility. Vaccine storage, administration and disposal will be documented by the Principal Investigator. Vaccine preparation and administration will be the responsibility of the Principal Investigator or deputy.

The objective is that 10 – 15 patients will be enrolled in the clinical trial. Both vaccines will be administered intra-muscularly (15 vials of each vaccine to be used

for vaccination). The AdCh3-NSmut1 vaccine will be administered on day 0 followed by the MVA-NSmut vaccine 8 weeks later. The injection site will be covered with a sterile dressing post vaccination and the patient will remain under observation for one hour in case of any immediate adverse effects. Patients will be released on the day of vaccination with instructions for notifying any symptoms experienced. Patients will be reviewed in the clinic on days 1, 7, 14 and 28 and by telephone 3 days post vaccination.

Worker protection measures taken during the release

Administration of the recombinant vector will be performed by a medical professional. In accordance with Clinical Research Facility protocol the medic will wear a disposable apron, clean gloves and protective eyewear during vaccine administration. However, conditions 5.2 and 6.1 require the implementation of SOPs relating to the handling of the GMO within the research facility and worker protection measures respectively.

Waste treatment

The autoclave used for the treatment of waste is situated in the containment level 2 laboratory in the Clinical Research Facility in St James's Hospital. All materials in contact with the vaccine or vaccination site will be disposed of in a suitable container for autoclaving. All sharps material will be disposed of in a sharps bin for autoclaving in-house. Waste will be autoclaved at 121^{o}C at 1.4 bar for a minimum of 15 minutes. Biological indicators will be used at least monthly in order to validate inactivation. Unused vaccine left in used vials will be placed in a sharps box and autoclaved on the same day.

Any spillages will be treated with disinfectant powder which will be left for 5 minutes to absorb all the liquid before clearing up with absorbent material which will also be autoclaved. The area will be washed with a broad spectrum disinfectant followed by washing thoroughly with water.

Any work surfaces that have potentially come in contact with the vaccine will be cleaned using Virkon solution.

Duration and frequency of monitoring

Patients will be monitored throughout treatment by the Principal Investigator and clinical trial staff in order to assess vaccine safety.
AdCh3-NSmut – Patients will have 12 clinical visits over a period of 8 months.

Following the administration of each vaccine the patient will remain under observation for one hour in case of any immediate adverse effects. Patients will be released on the day of vaccination with instructions for notifying any symptoms experienced.

Representations made in respect of the notification

Any person may make a representation in respect of matters relating to the deliberate release of the GMO 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, S.I. No 500 of 2003. The notice was published in "The Southside People" newspaper (circulating in the area of St James's Hospital) on 16 April 2014, and the period for submission of representations ended on 13 May 2014. The Agency received no representations during this period.

Review of the notification by the EPA and external consultation

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

External Review

View of the GMO Advisory Committee

The GMO Advisory Committee

The Agency consulted the GMO Advisory Committee (GMO AC) on this application and received 5 replies none of which expressed any concern provided all procedures are followed as stated.

Consultation with other regulatory bodies and government departments

The Agency informed the Irish Medicines Board (IMB) of the proposed deliberate release. The IMB has also received an application in respect of this proposed use which is currently undergoing review.

Other EU member states

As previously stated the Agency submitted the Summary Information Notification Format (SNIF) to the Commission. The Commission published the SNIF to all other EU member states for comment (02/05/2014). 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 received.

Site Inspection

The Agency inspected the Clinical Research Facility in St James's Hospital on 19 June 2014. The vaccine will be received and held at -80^{o}C within the dispensary. The vaccine will be drawn up into a syringe within a containment level 2 (CL2) facility. This procedure will be performed on a stainless steel procedure trolley in order to minimise handling of the vaccine up to the time of patient administration which will take place next door in the day ward. Minimum waste will be generated at the patient's bedside and all materials in contact with the vaccine or vaccination site will be autoclaved immediately afterwards.

All procedures will be performed in accordance with in-house procedures and will be checked and verified by two members of the clinical team.

Conclusions

After examining the information provided in the notification under Article 14 of the GMO (Deliberate Release) Regulations S.I. No 500 of 2003 and the further information provided by the notifier in response to a request from the Agency under article 19(1), OCLRR conclude that this notification is in compliance with the aforementioned Regulations.

The purpose of the deliberate release is the transient expression of a Hepatitis C antigen produced by two vaccine candidates in HIV-1 patients on antiretroviral therapy.

- AdCh3NSmut1 is a modified recombinant chimpanzee adenovirus derived from an attenuated replication incompetent adenovirus. The recombinant virus is not able to replicate or integrate into the human genome and so its presence will be transient;

- MVA-NSmut is produced with a highly attenuated Vaccinia viral strain that does not replicate efficiently in mammalian cells.

Both vectors are genetically modified to promote the expression of Hepatitis C immunogen NSmut.

Given the inability of the viral vectors to replicate in mammalian cells the potential for environmental impact or an impact on human health is negligible.

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 that the risks posed to the environment and human health (general population) by the deliberate release of this GMO are negligible.

On this basis I recommend that consent be granted to the GUIDE Department, St James's Hospital, Dublin 8 to conduct a clinical trial under Part B of the GMO (Deliberate Release) Regulations to assess the safety and immunogenicity of recombinant Hepatitis C vaccines in Hepatitis C unaffected, HIV-1 seropositive individuals at the Wellcome Trust-HRB Clinical Research Facility, St James's Hospital, Dublin 8 from the date of grant of consent conditions by the Agency to 31 December 2015 subject to the conditions set out in the attached draft Consent Conditions.

Signed: B Murray Date: 26 June 2014

Bernie Murray
Inspector
Office of Climate, Licensing, Resources and Research